

National Institute on Alcohol Abuse and Alcoholism

## Alcohol and Health Monograph 2

# Biomedical Processes and Consequences of Alcohol Use



**U.S. DEPARTMENT OF HEALTH AND  
HUMAN SERVICES**

**Public Health Service**

**Alcohol, Drug Abuse, and  
Mental Health Administration**



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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service  
Alcohol, Drug Abuse, and Mental Health Administration

National Institute on Alcohol Abuse and Alcoholism  
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# Foreword

With the publication of the Alcohol and Health Monograph series, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) endeavors to present a current, comprehensive picture of the broad range of information available on alcoholism and alcohol abuse. The four monographs in the series illustrate the progress that has been made in recent years in all areas of alcohol-related activity.

The monograph on *Alcohol Consumption and Related Problems*, examines alcoholic beverage consumption and the nature of problems associated with consumption from various perspectives, including factors which may lead to alcohol-related problems.

Monograph No. 2, *Biomedical Processes and Consequences of Alcohol Use*, reviews current findings and developments in the field of alcohol-related research and describes the differential effects alcohol exerts on the major systems of the human body.

Monograph No. 3, *Prevention, Intervention and Treatment: Concerns and Models*, describes the three levels of response—primary, secondary, and tertiary—that have been developed to address problems resulting from alcohol use. This monograph reviews current approaches and strategies for prevention; presents the concept of and describes intervention activities; discusses treatment issues and methods; and enumerates currently available resources, as well as those evolving within the Federal, State, local and voluntary sectors to implement alcohol-related programs.

Monograph No. 4, *Special Population Issues*, provides a forum for examining the unique problems of special population groups whose need for alcoholism and alcohol abuse programs has been underserved. This monograph demonstrates that a base of scientific knowledge exists on prevalence, incidence and nature of alcohol-related problems of special population groups defined by sex, age, race and ethnicity.

The information contained in these documents represents the efforts of many experts and scientists in the field of alcoholism. We believe they will be of benefit and interest to the scientific and professional communities as well as the lay public.



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# **Chapter 1**



# Effect of Alcohol on Membranes

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## Abstract

Alcohol continues to be the most misused drug in the Nation. Although earlier studies concentrated primarily on the intoxicating effects of alcohol and on liver damage from its excessive use, it has become increasingly clear that all organs, tissues, and cells are affected by chronic exposure to alcohol. Alcohol and its metabolites, such as acetaldehyde, are toxic chemicals with numerous effects on cellular functions throughout the body. These effects are ultimately reflected in the gross changes observed in organs and tissues of alcoholic patients. Alcohol abuse is associated with increased incidence of many types of cancer, general myopathy, cardiomyopathy, brain damage and altered nerve functioning, liver damage, hormonal changes, and teratogenesis (fetal alcohol syndrome).

This review focuses on the cellular level, specifically on the cell's membranes, where all of these alcohol-related problems begin. Alcohol's primary site of action is the cellular membranes, which play a central role in cellular function by serving as a two-dimensional matrix for the organization of enzymes involved in multistep processes and as a means of compartmentalizing regions within the cell. These compartments, called organelles, are highly specialized for particular functions—for example, energy generation in the mitochondria, lipid and protein synthesis in the endoplasmic reticulum and Golgi complex, regulation of gene activity in the nucleus, and encapsulation of hydrolytic enzymes in the lysosomes and food vacuoles to protect the cell against self-digestion. All of these organelles are surrounded by membranes, and these membranes can be damaged by alcohol and its metabolites.

The cell itself is surrounded by the plasma membrane, which serves as the major permeability barrier separating the cell from its environment. The plasma membrane is a dynamic system: it is the site for sensory, hormonal, and physiological controls; the site of interaction with other cells, a critical factor in development and differentiation; and the site of entry of cellular nutrients and of excretion of cellular products. Alcohol has been shown to alter many membrane-associated processes such as permeability, uptake of nutrients, action of membrane-bound enzymes, and initiation and propagation of nerve impulses.

The ability of alcohol to interfere with cellular membranes is due to the fact that it is amphipathic. Amphipathic substances are those that can interact with both polar and nonpolar (hydrophobic) substances. Thus, while oil and water do not mix, alcohol can mix with either. The amphipathic nature of

alcohol allows it to be mixed with other ingredients in water (a polar substance) to make a highball, yet also to damage cellular membranes.

## ***Introduction***

Alcohol continues to be the most misused drug in the Nation. Although earlier studies concentrated primarily on the intoxicating effects of alcohol and on liver damage from its excessive use, it has become increasingly clear that all organs, tissues, and cells are affected by chronic exposure to alcohol.

Alcohol and its metabolites, such as acetaldehyde, are toxic chemicals with numerous effects on cellular functions throughout the body. These effects are ultimately reflected in the gross changes observed in organs and tissues of alcoholic patients. Alcohol abuse is associated with increased incidence of many types of cancer, especially in the mouth and esophagus; general myopathy (Rubin 1979); cardiomyopathy (Rubin 1979); brain damage and altered neural functions (Riley and Walker 1978); liver damage (Lieber et al. 1979); hormonal changes (Van Thiel and Lester 1976); and teratogenesis (fetal alcohol syndrome) (Mulvihill and Yeager 1976).

This review focuses on the cellular level, specifically on the cell's membranes: Membranes play a central role in cellular function by serving as a two-dimensional matrix for the organization of enzymes involved in multistep processes and as a means of compartmentalizing regions within the cell. These compartments, called organelles, are highly specialized for particular functions—for example, energy generation in the mitochondria, lipid and protein synthesis in the endoplasmic reticulum and Golgi complex, regulation of gene activity in the nucleus, and encapsulation of hydrolytic enzymes in the lysosomes and food vacuoles to protect the cell against self-digestion. All of these organelles are surrounded by membranes, and these membranes can be damaged by alcohol and its metabolites.

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ingredients in water (a polar substance) to make a highball, yet also to damage cellular membranes.

Indeed, the potency of ethanol, other alcohols, and a variety of anesthetic drugs in affecting many biological phenomena correlates with their solubility in lipids (Hill and Bangham 1975; Ingram 1976; Jain et al. 1978). This does not mean that ethanol and the other drugs act by the same mechanism, only that hydrophobic sites are involved in their mechanism of action.

## ***Membrane Organization and the Effects of Ethanol***

Enormous progress in understanding membrane organization has been made in recent years. Animal cell membranes are now known to be composed primarily of phospholipids, cholesterol, and proteins (Quinn 1976). Although membranes from different organelles within the same cell and from different tissues within the same organism vary widely in the proportions of these components, there is considerable similarity between equivalent organelles and tissues of different organisms. This indicates that membrane composition is specialized for particular functions (Quinn 1976). In this regard, the membranes of nerve cells, which carry out unique functions, contain the most complex assortment of polar lipids found among body tissues.

All cellular membranes are organized as a lipid bilayer with the polar heads of lipids facing outward (Singer and Nicolson 1972). This bilayer is asymmetric (Op den Kamp 1979); that is, the various types of lipids are unequally distributed on the inner and outer face of the bilayer. Within this two-dimensional array of lipids, sterols and membrane proteins are embedded. Proteins are also distributed asymmetrically across the bilayer. The polar lipids immediately surrounding membrane proteins are organized to some extent by their lateral interactions with the proteins (Hesketh et al. 1976; Jost et al. 1973; Sen and Ray 1979). These lateral interactions are in some cases quite specific and involve both polar and nonpolar interactions. Ethanol, an amphipathic molecule, is capable of affecting all of these associations.

Membranes in living cells appear to be in a fluid state (Singer and Nicolson 1972), allowing the lipid molecules and protein molecules to be in constant motion (Austin et al. 1979; Cherry 1979; Devaux and McConnell 1972; Smith et al. 1979). How free this motion is depends on the fluidity of the membrane (i.e., how low its viscosity is). Although membrane fluidity, which appears to be essential for cellular function (Cronan 1978; Cronan and Gelman 1975) and is affected by all membrane components, the fatty acid composition of membrane phospholipids appears to have an especially important role.

The phospholipid molecules in the membrane contain mixtures of fatty acids that vary in their number of double bonds and in chain length, but basically they are of two kinds—saturated and unsaturated. The



proportions of these various kinds of fatty acids affect membrane fluidity in much the same way that they determine the fluidity of shortenings used for cooking. Thus unsaturated fatty acids (like those found in vegetable oils, e.g., "Mazola") contain many double bonds and tend to increase the fluidity of membranes (Baldassare et al. 1976, 1977), while saturated fatty acids (like those found in solid shortenings, e.g., "Crisco") tend to decrease cell membrane fluidity. Longer fatty acids also tend to make membranes less fluid.

In cellular membranes, the proportions of saturated and unsaturated fatty acids change with growth temperature (Cronan 1978; Cronan and Gelman 1975; Fulco 1974). These changes are considered adaptive; that is, as the temperature changes, the proportions of saturated and unsaturated fatty acids are altered to maintain fairly constant membrane fluidity (Sinensky 1974). Sterols are lipids that also help to maintain constant membrane fluidity by acting as fluidity buffers (Pang and Miller 1978); that is, they tend to make fluid membranes less fluid (i.e., increase their viscosity) and rigid membranes more fluid (i.e., reduce their viscosity) (Quinn 1976). The regulation of membrane fluidity by changing lipid composition appears to be a common feature of cells in animals, plants, and bacteria (Fulco 1974).

A sharp fluidity gradient exists across the width of the membrane (Quinn 1976). Other gradients such as charge density and polarity also span the membrane width. Various kinds of proteins interact with these gradients as well as with the polar and nonpolar components of lipid molecules. The specific location and orientation of a protein molecule in the membrane represents a dynamic equilibrium between these complex interactions. Alcohol and other drugs have the potential of disturbing this equilibrium by affecting any one of the factors associated with it.

Cell membranes are freely permeable to alcohol (Kalant 1971). And even though alcohol is a relatively polar molecule capable of extensive hydrogen bonding, to a small extent it can associate with molecules in cell membranes. This association has been measured directly in artificial membranes (Hill 1978), neural membranes (Grenall 1975), and membranes from other tissues (Seeman 1972).

Physically, the interaction of physiologically relevant levels of alcohol with membranes causes a small increase in membrane fluidity (Chin and Goldstein 1977a, b; Grisham and Barnett 1973; Hill 1978; Jain et al. 1978; Johnson, Lee, and Cooke 1979; Johnson, Lee, Cooke, and Loh 1979; Lee 1976a, b; MacDonald 1978; Vanderkooi 1979). The increase is equivalent to that produced by a temperature increase of less than 1, C. This change in bulk fluidity may be related to biological processes such as the anesthetic effect (Chin and Goldstein 1977; Richards et al. 1978). These changes cannot be expected to account for all alcohol-induced alterations in membrane function, considering the diversity of lipids and proteins within the membrane, the asymmetry of their distribution across a bilayer, and their many specialized functions.



Nevertheless, this interaction does demonstrate that ethanol directly affects the organization of the membrane.

Clearly, the membranes of cells are complex structures with many components in dynamic equilibrium. Since for any specific biological process a single rate-limiting component must exist, the observed effects of alcohol on the overall process are the result of its direct effects on the rate-limiting component or on that component's interaction with its environment. The rest of this review deals with these more specific effects of alcohol on membrane function.

## ***Active Transport and the Effects of Ethanol***

One of the many important functions of the cellular membranes is the uptake of nutrients and other molecules by active transport systems. (Active transport, in contrast to passive diffusion, involves chemical mechanisms and the expenditure of energy to move molecules through a membrane.) During the past few years, considerable progress has been made in our understanding of active transport and its relationship to ion flows, ion gradients, and differences in electrical potentials between opposite sides of membranes.

These ion flows and differences in electrical potential have long been recognized in nerve tissue as the molecular events that give rise to the action potential, or nerve impulse (Kalant 1975; Palay and Chan-Palay 1975; Whittaker 1973, 1975). However, they are now recognized as the basic mechanism by which all cells interconvert chemical and potential energy. In this view, the ion flows that occur during the propagation of an impulse in nerve cells are but a specific application of activities common to all cells (Kehoe 1975).

The energy for numerous cellular processes such as active transport, nerve impulses, and the movement of cilia is now known to be derived from the coupling of electric currents and currents of sodium ions ( $\text{Na}^+$ ), potassium ions ( $\text{K}^+$ ), calcium ions ( $\text{Ca}^+$ ), and magnesium ions ( $\text{Mg}^+$ ). The plasma membrane itself couples ion flows to provide energy for particular cellular functions such as the uptake of nutrients.

Ethanol has a variety of effects on the uptake of molecules by cells (Shanbour 1979; Sun et al. 1977; Wilson and Hoyumpa 1979), but generally it increases the permeability of cells to ions and organic molecules. The concentrations of ethanol required to affect active transport processes and cellular permeability are much higher than are required to depress the functioning of the central nervous system and are more similar to the levels used to cause local anesthesia.

Active transport processes are affected in different ways by alcohol. In liver cells (hepatocytes) ethanol stimulates some active transport systems, for example, the uptake of 5-methyl-tetra-hydrofolic acid (Horne et al. 1979). However, in a variety of tissues most transport systems are inhibited by ethanol. For example, in the intestine ethanol

inhibits the uptake of 3-O-methyl glucose, amino acids, and vitamins (Hoyumpa et al. 1978; Kuo and Shanbour 1979; Wilson and Hoyumpa 1979). In nerve tissue, it inhibits the transport of  $\text{Na}^+$  ions, lysine, alpha-aminobutyric acid, and other compounds (Choy et al. 1972; Roach et al. 1973; Tabakoff et al. 1975).

While the mechanism and energy coupling of all of these transport systems is not fully understood, transport systems that are coupled to the movement of  $\text{Na}^+$  across the membrane are particularly sensitive to inhibition by ethanol (Choy et al. 1972; Roach et al. 1973). The  $\text{Na}^+$  gradient across the membrane is generated by an enzyme called ATPase, which is located within the membrane and uses energy derived from the hydrolysis of adenosine triphosphate (ATP), an important compound used by living organisms to store chemical energy for use in numerous functions.

In nerve cells the  $\text{Na}^+$  gradient is needed to propagate nerve impulses. Although concentrations of ethanol that induce local anesthesia inhibit ATPase (Sun et al. 1977), this inhibition is probably not responsible for the immediate effects of ethanol on transport since  $\text{Na}^+$  ion gradients are dissipated slowly during normal transport. Thus even after ATPase is inhibited by ethanol, the gradients would tend to persist for a while. The persistence of the gradients after ethanol administration requires an alternative explanation for the immediate effects of ethanol. Alternative effects are discussed in the next section.

## ***Nerve Cell Function and the Effects of Ethanol***

### ***Synaptic Transmission***

Nerve cells have complex functions. In addition to carrying out the routine physiological activities of transport and metabolism common to all cells, they are specialized for the initiation and conduction of nerve impulses.

Each nerve cell has a long filamentous extension, the axon, at one end and several short processes, the dendrites, at the other. Nerve cell networks are formed by the axons of nerve cells terminating close to the dendrites of other nerve cells. A nervous impulse in a single nerve cell begins at the dendrites and travels to the tip of the axon. From there it is usually relayed to the dendrites of the next nerve cell by means of chemical messengers called neurotransmitters, which diffuse across a small gap called the synaptic cleft and trigger a nervous impulse in the next cell.

Membranes play an important role in nerve cell function. For example,  $\text{Na}^+$ -coupled transport of nutrients causes changes in axon membranes that are similar in some ways to those caused by neurotransmitters (Kehoe 1975). The dendrites have club-shaped processes called postsynaptic terminals which contain membrane structures. These are aligned with specialized regions called presynap-

tic terminals at the tip of the axons of adjacent nerve cells (Palay and Chan-Palay 1975; Whittaker 1973, 1975). The pre- and postsynaptic terminals are separated by the synaptic cleft. The postsynaptic terminal contains the receptors for neurotransmitters (Davies et al. 1980; Hucho et al. 1976; Pant et al. 1979; Tarrab-Hazdai et al. 1980; Witzemann and Raftery 1978), which are secreted at the presynaptic terminal and diffuse across the synaptic cleft.

There are several neurotransmitters, but acetylcholine is the best-studied one and is used here to illustrate the principle of synaptic transmission and the important role that membranes play in the process (the other neurotransmitters are beyond the scope of this review). On activation by a nerve impulse, vesicles containing acetylcholine within the presynaptic terminal of one nerve cell fuse with that cell's plasma membrane, releasing the neurotransmitter into the synaptic cleft. Acetylcholine then diffuses across the synaptic cleft and binds to the specialized receptors on the external surface of the postsynaptic terminal of the adjacent cell. The binding of these neurotransmitter molecules in some way leads to changes in the properties of the postsynaptic membrane, and this in turn triggers a breakdown in the selective permeability of the postsynaptic membrane and a resulting change in the membrane's potential.

During this transient change in permeability,  $\text{Na}^+$  ions flow into the postsynaptic terminal and potassium ions ( $\text{K}^+$ ) move into the synaptic cleft. The transient change in permeability spreads as a wave from the point of initiation throughout the plasma membrane. In elongated cells this appears as a unidirectional propagation—the nerve impulse, or action potential—which moves from the dendrites to the cell body to the tip of the axon.

When the nerve impulse reaches the presynaptic terminal at the tip of the axon, it causes the vesicles in the terminal to release acetylcholine, thus initiating the same sequence of events in an adjacent cell. In this manner, a nerve impulse originating in one nerve cell can be passed along to many others.

In some cases there is no synaptic cleft, and adjacent cells have tight junctions. In such junctions the nerve impulse is transmitted directly from the membrane of one cell to another without the involvement of vesicles or neurotransmitters.

The energy for the transmission of a nerve impulse is ultimately derived from the conversion of chemical energy from cytoplasmic molecules to potential energy in the form of ion gradients. The gradients are formed by pumping hydrogen ion ( $\text{H}^+$ ), calcium ion ( $\text{Ca}^+$ ), and  $\text{Na}^+$  out of the cell while concentrating  $\text{K}^+$  and magnesium ion ( $\text{Mg}^+$ ) within the cytoplasm.

$\text{Ca}^+$  is known to play a unique role in the fusion of vesicles, and its buildup (either by influx or by its release from some internal reservoir) is thought to be critical for the release of neurotransmitter (Curran and Seeman 1979; Erickson et al. 1978; Rahaminoff et al. 1975; Ross 1977; Ross et al. 1979; Rubin 1970).



After synaptic transmission has occurred, acetylcholine is chemically broken down by the enzyme acetylcholinesterase to form choline, an inactive compound that is released from the receptors in the postsynaptic terminal. Choline is then concentrated within the presynaptic terminal by active transport processes. Finally, acetylcholine is resynthesized from choline and is again packaged into vesicles for reuse in the next synaptic transmission. Both the presynaptic and postsynaptic membranes use high energy compounds and membrane-bound ATPase enzymes to fully regenerate the difference in ion concentrations between the inner and outer sides of their plasma membranes.

Membranes are involved in every step of this process. First, the plasma membrane serves as a barrier to allow the generation of differences in ion concentration between the cytoplasm and the surroundings. Second, the ATPase enzymes that pump these ions are themselves embedded within the synaptic plasma membrane (Sen and Ray 1979), as are the proteins that catalyze the active uptake of choline for reuse (Lefresne et al. 1977). Third, neurotransmitters are encapsulated in specialized membrane vesicles and are released in a controlled fashion by fusing with the plasma membrane of the presynaptic terminal (Whittaker 1973). Fourth, the synaptic cleft is bounded by the external faces of the plasma membranes. Fifth, neuroreceptors are embedded in the membrane of the postsynaptic terminal and face outward for binding to neurotransmitters. Sixth, once activated, these receptor-neurotransmitter complexes trigger some as-yet-undetermined structural changes that result in the transient and partial disruption of the plasma membrane permeability barrier. Finally, this perturbation is laterally propagated along the membrane. Ethanol could alter neural function by affecting any one of these membrane-associated steps.

### *Effects of Ethanol on Synaptic Transmission*

Over 70 years ago, Meyer and Overton (Hill 1978; Seeman 1972; Seeman and Lee 1975; Seeman et al. 1970) demonstrated that the potency of a wide variety of anesthetics and central nervous system depressants, including ethanol, is directly correlated with their solubility in lipids. They proposed that the mechanism of action of all such agents is their physical incorporation into the lipids of cell membranes, a process that expands the membranes. Consistent with this hypothesis is the fact that the effects of ethanol in animals can be reversed by subjecting them to high atmospheric pressures (Halsey and Wardley-Smith 1975; Johnson and Flagler 1950; Miller et al. 1973; Trudell et al. 1973). This unified hypothesis has had a major influence on research on the mechanism by which alcohol and many other drugs affect nerve function (Freund 1979a, b).

Measurement of the effects of ethanol on nerve function is complicated by the variety of functions used as indices of effectiveness, the variety of systems employed, the diversity of tissues and receptors involved, and the complexity of the neurotransmission process itself.

Many studies have employed large neurons, but high concentrations of ethanol are required to produce observable changes in such systems (Kalant 1975). Studies of ethanol as a local anesthetic are thought to be relevant to depressive effects of ethanol on the central nervous system, but the precise relationship between these two activities is not fully understood. As a result, it has been very difficult to investigate the molecular mechanisms of central nervous system depression by ethanol.

In studies using brain tissue, biological effects have been observed with much lower concentrations of ethanol than are required to produce local anesthesia (Freund, 1979*b*). Ethanol does not induce narcosis or block neural function by inhibiting the synthesis of acetylcholine or its packaging into synaptic vesicles (Kalant et al. 1967, 1971). Nor does it appear to inhibit the fusion of the vesicles in the presynaptic terminal. On the contrary, it appears to increase the rate of spontaneous fusion of the vesicles (Curran and Seeman 1979; Quastel et al. 1970; Velussi et al. 1979).

In experiments with electrical stimulation of nerve cells, ethanol increases the amount of electrical stimulation required to elicit a nerve impulse. This appears to be due to increased resistance of the membrane and decreased conductance of  $\text{Na}^+$  on activation (Armstrong and Binstock 1964; Bergmann et al. 1972; Eidelberg and Wooley 1969; Gage 1965; Houck 1969; Knuttsson and Katz 1967; Moore et al. 1964; Nikander et al. 1971). The amount of acetylcholine released by electrical stimulation is also lower in the presence of ethanol (Kalant 1975). Since it has been shown that ethanol increases the rate of spontaneous fusion of the vesicles containing acetylcholine, this inhibition of electrically induced acetylcholine release may mean that ethanol interferes with the production of an activated state required for membrane fusion, rather than with fusion itself.

Ethanol would not be expected to affect the rate of diffusion of neurotransmitters across the synaptic cleft. In most cases, ethanol has little effect on the affinity of acetylcholine receptors in the postsynaptic terminal and does not inhibit the breakdown of bound acetylcholine by acetylcholinesterase (Kalant et al. 1967). In one study, however, ethanol was reported to inhibit acetylcholinesterase in isolated synaptosomes from guinea-pig brain (Sun and Samorajski 1970). Ethanol has been reported to have variable effects on other neurotransmitter receptors (Fairhurst and Liston 1979; Hunt et al. 1979; Liljequist and Engel 1979). The uptake of choline released into the synaptic cleft and its use in the resynthesis of acetylcholine by the presynaptic terminal are not inhibited by ethanol (Hunt et al. 1979; Kalant et al. 1967).

The ATPase enzymes that regenerate the ion gradient are slightly inhibited by ethanol (Jarnefelt 1961; Sen and Ray 1979; Sun et al. 1977; Wallgren et al. 1975). However, this inhibition has little effect on the resting potential of nerve cells and does not appear to be involved significantly in the effects of ethanol (Richards et al. 1978).

Thus the anesthetic activity of ethanol does not result from secondary effects on either the ion gradients or neurotransmitter molecules. Instead, ethanol's primary effects—decreased ion flow and decreased neurotransmitter release—appear to involve direct effects on synaptic transmission.

A larger action potential is observed in many nerves when they are restimulated shortly after firing. The enhancement, called post-tetanic potentiation (Traynor et al. 1976), is thought to result from organizational changes induced by the initial stimulation that have not returned to the resting state before the second stimulation. Post-tetanic stimulation decays slowly and with repeated activation it can often be observed for hours. Ethanol, however, causes post-tetanic potentiation to decay rapidly (Barondes et al. 1979; Traynor et al. 1976, 1979).

A variety of models have been proposed to explain this mechanism of action of ethanol on synaptic transmissions. All models agree that synaptic membranes are the primary sites for the action of ethanol and that ethanol exerts its effects by disturbing some aspect of organization within the membrane (Abood and MacNeil 1979; Barondes et al. 1979; Boggs et al. 1976; Chin et al. 1979; Curran and Seeman 1979; Freund 1979a, b; Goldstein 1978; Hill and Bangham 1975; Johnson, Lee, and Cooke 1979; Johnson, Lee, Cooke, and Loh 1979; Lee 1976a, b; Littleton 1978; Littleton and John 1977; Littleton et al. 1979; Ross et al. 1979; Trudell 1977; Vanderkooi 1979).

As mentioned earlier, the correlation between lipid solubility and anesthetic potency has been interpreted as evidence for a universal site or mechanism of action. In this regard, two general effects of the penetration of alcohols into hydrophobic regions of membranes have been found: membrane expansion and an increase in overall membrane fluidity (Freund 1979b; Goldstein 1978; Littleton et al. 1979). In addition, ethanol increases calcium binding to membranes (Curran and Seeman 1979; Ross 1977; Ross et al. 1979). The increased binding of calcium could result from changes in membrane organization induced by ethanol (Curran and Seeman 1979; Ross et al. 1979) and could have a major effect on the release of neurotransmitters by the fusion of synaptic vesicles.

On the other hand, some recent studies provide evidence that bulk membrane expansion and bulk changes in membrane fluidity may not be causally involved in the anesthetic effect of alcohols (Boggs et al. 1976; Franks and Lieb 1978; Richards et al. 1978; Vanderkooi 1979; Vanderkooi et al. 1978). Richards et al. (1978) found that while ethanol causes a small increase in membrane fluidity at anesthetic concentrations, equally potent concentrations of the anesthetic, dodecanol (a high molecular weight alcohol), cause a decrease in membrane fluidity. Furthermore, while the effects of these two alcohols on membrane fluidity are opposite, their anesthetic effects are roughly additive. Also, fluidity changes induced by anesthetic concentrations of ethanol are extremely small, equivalent to fluidity changes caused by less than 1



degree increase in temperature—and changes in temperature of 1 or 2 degrees neither cause nor relieve anesthesia (Franks and Lieb 1978).

The molecular site of action of ethanol within the membrane appears to have both polar and nonpolar characteristics (Boggs et al. 1976; Franks and Lieb 1978; Vanderkooi 1979). Protein/lipid complexes in the membranes have been proposed as the most likely candidates for this site of action (Boggs et al. 1976; Franks and Lieb 1978; Pant et al. 1979; Vanderkooi 1979). The compositional and organizational complexity of the neural membrane make it unlikely that a single global change in structure is involved. Despite the complexity of synaptic transmission, there must be a single rate-limiting step that is affected by ethanol, and this step must ultimately involve a minor proportion of the total components of the neural membrane. Both the lipid/protein complex that forms the  $\text{Na}^+$  channel (Lee 1976a, b; Richards et al. 1978; Strickholm 1978) and the membrane components involved in  $\text{Ca}^{++}$  binding and release (Curran and Seeman 1979; Ross et al. 1979) have been proposed as likely sites.

### *Tolerance and Dependence*

Chronic exposure to alcohol causes humans and experimental animals to become resistant to many of its effects. This acquired resistance, called alcohol tolerance (Himmelbach 1943), has been particularly well correlated with post-tetanic potentiation (Barondes et al. 1979),  $\text{Ca}^{++}$  binding (Ross et al. 1979), and micro-end plate potential (Curran and Seeman 1979).

Alcohol tolerance, which is not limited to neural tissues (Altura et al. 1980), is accompanied by decreased effectiveness of other drugs such as pentobarbital (Hill and Bangham 1975). The phenomenon is referred to as cross-tolerance. During the acquisition of tolerance, the enzymatic mechanisms for metabolizing ethanol (the microsomal oxidizing system) are enhanced (Lieber et al. 1979). However, this does not appear to be the basis of alcohol tolerance. Instead, alcohol tolerance results from changes in the nervous system that allow nerve cells to function more normally in the presence of ethanol (Kalant 1975).

Alcohol tolerance is often accompanied by physical dependence, although the precise relationship between these two states is unknown. Dependence is thought to result from changes in nerve tissues, presumably for the accommodation of ethanol, that are so extensive that neural function is impaired by the sudden removal of ethanol. Clinically, dependence is observed during withdrawal. If not controlled, the withdrawal process itself can cause the death of alcoholic patients.

Since the membranes of neural cells are viewed as the primary site of action of ethanol and other anesthetics, investigators have examined the effects of ethanol on neural membranes to determine the molecular basis of tolerance and dependence. Membranes from tolerant organisms have been found to have some resistance to the fluidizing effects of ethanol (Goldstein 1978).

Changes in neural membrane composition have also been found in tolerant organisms. These include increases in the exposed sialic acid of glycoproteins (Noble et al. 1976) and in anionic (negatively charged) lipids (Abood and MacNeil 1979; Wallgren et al. 1975). These changes may be involved in the altered  $\text{Ca}^{+}$  binding observed in tissues from dependent animals (Abood and MacNeil 1979; Puskin and Martin 1978; Ross 1977). Changes have also been observed in the proportion of unsaturated and saturated fatty acids in polar lipids, although conflicting findings have also been reported. Littleton and co-workers (Littleton 1978; Littleton and John 1977; Littleton et al. 1979) found significant decreases in fatty acid unsaturation in dependent individuals. Others (French et al. 1971; Spach et al. 1979; Sun and Sun 1979) found the opposite effect of increased unsaturation. This disagreement may be due in part to the difficulty of measuring the extremely labile long-chain fatty acids and the large diversity of fatty acids present in neural lipids.

Tolerant organisms also have elevated levels of cholesterol in their neural membranes (Chin et al. 1978; Goebel et al. 1979). However, elevated cholesterol alone probably is not the basis of tolerance (Johnson, Lee, and Cooke 1979; Johnson, Lee, Cooke, and Loh 1979), although it may be involved in the tolerance-related effects of ethanol on membrane viscosity and  $\text{Ca}^{+}$  binding (Chin and Goldstein 1977a; Pang and Miller 1978).

Several indirect mechanisms that may alter the sensitivity of synaptic transmission in response to stimulus—including hormonal levels, receptor levels, and neuromodulators—may be involved in the development of tolerance and dependence. Complex changes in these factors in response to chronic ethanol exposure have been described (Bhalla et al. 1979; Freund 1979b; Seeman and Lee 1975; Tabakoff et al. 1978). Dopamine receptors and dopamine levels are of particular interest in this regard, because they follow trends during the development and loss of tolerance that suggest a direct relationship (Tabakoff and Hoffman 1978, 1979). In the whole organism, these more complex interactions may be particularly important for both tolerance and dependence. A number of other membrane-related systems have been shown to decrease in their responsiveness to ethanol during the development of tolerance. These include the muscarinic-cholinergic acceptors from mouse brain (Tabakoff et al. 1979), the synaptosomal glutamate-binding proteins (Michaelis et al. 1978), and the synaptosomal ( $\text{Na}^{+}$ - $\text{K}^{+}$ ) ATPase (Leventhal and Tabakoff 1980).

### ***Membrane Associated Protein Synthesis and the Effects of Ethanol***

Ethanol has been shown to produce gross changes in morphology and composition in the liver (Orrego et al. 1979; Seymour and Peters 1978), heart and skeletal muscles (Rubin 1979), intestine (Eloy et al.

1979; Fox et al. 1979), and other tissues. The changes include alterations in protein synthesis.

Ethanol has been shown to affect protein synthesis by inhibiting the synthesis of messenger RNA molecules in the nucleus of brain tissues and by retarding their transport to the cytoplasm for translation (Tewari and Noble 1977). [Note: A brief description of the role of messenger RNA and the process of translation in the synthesis of protein is provided in the paper by Murray Oratz in this volume.] Such changes in other tissues could alter the levels and types of protein synthesized.

Ethanol may also affect protein synthesis directly by interfering with cell membranes involved in the process. Membranes are known to be intimately involved in the synthesis of many types of protein, including secretory proteins, glycoproteins, and integral membrane proteins (Frazier and Glaser 1979). The polypeptide portions of secretory proteins and integral membrane proteins are partly synthesized by the polysomes of the endoplasmic reticulum, a membranous structure. After they are synthesized, these polypeptides are often modified by other systems to produce the final protein product and are then transported to organelles called the Golgi bodies, which have membranous boundaries. In the Golgi bodies, carbohydrate components are added to some proteins (the process is called glycosylation) to make glycoproteins, while other proteins are packaged in membrane-bounded vesicles for delivery to the plasma membrane or for excretion (Davies and Tai 1980; Morre' et al. 1979).

In addition, many of the glycoproteins are inserted into the plasma membrane where they serve as recognition molecules. Glycoproteins have structural characteristics that allow them to be "recognized" by regulatory substances and to serve as receptors for them; they are involved in hormonal interactions and in cell-to-cell interactions for regulation of cell division, growth, and differentiation (Frazier and Glaser 1979). Thus these regulatory processes may be affected indirectly by the effects of ethanol and its metabolites on the synthesis or processing of the membrane-bound receptors.

Acute administration of ethanol has been shown to depress the rates of synthesis and secretion of albumin, fibrinogen, and transferrin in mammalian liver tissue (Challakonda et al. 1980; Jeejeebhoy et al. 1972; Kirsch et al. 1973; Rothschild et al. 1974). Chronic exposure to alcohol depresses the levels of these proteins in serum (Orrego et al. 1979).

Membrane-bound proteins are also affected by chronic exposure to alcohol. For example, chronic exposure to ethanol alters the levels of membrane-bound dopamine receptors of neural tissues (Tabakoff and Hoffman 1978; Tabakoff et al. 1978) and membrane-bound gonadotropin receptors in the testes (Bhalla et al. 1979). Also, the levels of intestinal membrane-bound disaccharidases (enzymes that digest a class of sugars called disaccharides) are reduced by chronic exposure to ethanol (Eloy et al. 1979). Chronic alcohol exposure (by reducing the levels of intestinal proteins involved in nutrient transport) and acute



alcohol exposure (by directly inhibiting the absorption of nutrients) may be involved in the nutritional deficiencies associated with alcohol abuse (Dinda et al. 1979; Hoyumpa et al. 1978).

In studies using bacterial cells as models, two local anesthetics have been shown to affect the synthesis and translocation of specific proteins made by membrane-bound polysomes (organelles of protein synthesis) (Di Rienzo and Inouye 1979). In *Escherichia coli*, benzyl alcohol blocks the transport and post-transcriptional processing of several major outer membrane proteins (Halegoua and Inouye 1979). In the same bacteria, procaine has been shown to block the processing and secretion of alkaline phosphatase (an enzyme involved in the breakdown of organic molecules containing phosphate groups) (Lazdunski et al. 1979). When the bacteria are exposed to these anesthetics, the affected proteins accumulate in precursor form within the plasma membrane. In my laboratory, we have recently observed numerous changes in the membrane proteins of *E. coli* when the bacteria are grown in the presence of ethanol. Some of the protein alterations may be due to accumulation of precursor forms.

In humans, some of the diverse effects of ethanol on tissues could result from fundamental effects of ethanol on the common biosynthetic process for excreted proteins and membrane proteins. Since surface membrane proteins play essential roles in cell-to-cell interaction during development (Frazier and Glaser 1979), changes in these proteins in a human embryo or fetus may lead to irreversible damage and contribute to the fetal alcohol syndrome.

### ***Alcohol Effects on Unicellular Organisms (Bacteria, Yeast, Protozoa, Cultured Mammalian Cells)***

Much of our knowledge of the physiology of differentiated and highly specialized mammalian cells was initially derived from investigations of the physiology of microbes. Despite the many differences between microbes and higher organisms, the existence of many fundamental similarities allows microbes to be used as model systems. These similarities include the bulk of biosynthetic and catabolic (breakdown) processes, the interconversion of chemical energy and potential energy using ion gradients, the coupling of ion gradients to the transport of nutrients, the biosynthetic mechanisms for macromolecules, and the extensive use of membranes for the organization of specific cellular functions (although in comparison with mammalian cells the membranes of microbes are extremely simple).

Bacterial cells have been shown to change their lipids during growth in the presence of alcohols (Ingram 1976; Sullivan et al. 1978). Most of my studies have dealt with *Escherichia coli*, a bacterium that produces ethanol as one of its major fermentation products but is unable to use it

as a carbon source (Chesbro et al. 1979). As a natural product, ethanol is a compound to which *E. coli* may have evolved an adaptive response.

Ethanol causes small changes in the viscosity of *E. coli* membranes, inhibits some transport processes (Ingram et al. 1980), causes a dose-dependent inhibition of growth, and, under appropriate conditions, kills cells (Fried and Novick 1973). The concentrations of ethanol that produce these effects are similar to those employed in studies of its local anesthetic effects in higher animals.

Many changes in membrane composition have been observed during growth of *E. coli* in the presence of ethanol, including an increase in anionic (negatively charged) lipids (Ingram 1977), an increase in the proportion of unsaturated fatty acids (Ingram 1976) and of phospholipids containing two unsaturated fatty acids (Berger et al. 1980), changes in the proportion of membrane proteins, and changes in peptidoglycan structure (Ingram and Vreeland 1980; Ingram 1981). We have investigated the mechanism by which ethanol induces changes in fatty acid composition and have found that the increased abundance of the unsaturated forms is primarily due to preferential inhibition of enzymes needed in the synthesis of the saturated forms (Buttke and Ingram 1978, 1980).

Some or all of these ethanol-induced changes may be adaptive. For example, although ethanol at first strongly inhibits the growth of these bacteria, the inhibition eventually diminishes, suggesting that adaptive changes may occur (Ingram 1976). Similarly, Clark and Beard (1979) found that *E. coli* mutants isolated for ethanol resistance overproduced anionic lipids and that membranes isolated from these mutants were much more resistant to disruption by ethanol than the parent strain.

Our studies provide evidence that the increase in unsaturated fatty acid may also be adaptive. In *E. coli*, drugs such as pentobarbital (to which alcoholics are often cross-tolerant) induce changes similar to those produced by ethanol (Ingram et al. 1978). Mutants unable to change their lipid composition in response to ethanol are also extremely susceptible to growth inhibition or death from exposure to ethanol. However, under conditions that restore the ability of these mutants to increase their unsaturated fatty acid production, their growth rate in the presence of ethanol becomes equal to that of normal strains. When *E. coli* were grown in the absence of ethanol, but under conditions that allowed their fatty acid composition to be controlled, manipulations that increased the proportion of unsaturated fatty acids enhanced survival when the bacteria were later transferred to buffered solutions of ethanol (nongrowing conditions). Conversely, manipulations that increased the proportion of saturated fatty acids made the bacteria extremely vulnerable to ethanol.

Many studies with other organisms implicate lipids and membranes as major sites for changes associated with resistance to ethanol. Recent studies by Thomas et al. (1978) with the yeast *Saccharomyces cerevisiae* have demonstrated that membrane lipids are involved in the resistance of yeast cells to killing by ethanol. The incorporation of

sterols that decreased membrane viscosity increased the resistance of *S. cerevisiae* to ethanol. In contrast, sterols that increase membrane viscosity under biologically relevant conditions (such as cholesterol) made the cells hypersensitive to killing by ethanol. The investigators also found that increases in the degree of unsaturation of membrane lipids were accompanied by increased survival of the yeast cells in ethanol solutions. In this connection, studies on the production of the alcoholic beverage sake by \**Saccaromyces* have shown that obtaining a brew with high alcohol content requires increased availability of lipids containing unsaturated fatty acids (Hayashida et al. 1974).

The bacterium *Lactobacillus heterohiochi*, the most alcohol-resistant organism known, contains unusual lipids in its membrane, primarily very long unsaturated fatty acids (Uchida 1974). Changes in fatty acid composition have also been observed in the protozoan *Tetrahymena pyriformis* when it is grown in solutions containing ethanol (Nandini-Kishore et al. 1979). Like *E. coli* (Ingram 1976), *Tetrahymena* increases the degree of unsaturation in its membrane lipids. Growth with phenethyl alcohol results in similar changes in *Tetrahymena* (Nozawa et al. 1979).

Thus membrane lipid changes are associated with alcohol resistance in yeast, bacteria, and protozoa. While many of these changes in the membrane lipids of microorganisms are in response to levels of ethanol far greater than those needed to produce central nervous system depression in humans, the diversity of organisms that show these responses suggests that they may be important.

Little work has been done on the effects of ethanol on cultured mammalian cells, perhaps because interpretation of results is made difficult by the complex relationship between nutrient composition and membrane composition in these systems. Ethanol has been shown to inhibit the proliferation of cultured lymphocytes (Freund and Forbes 1976). Studies in my laboratory have shown that cultured mammalian cells develop modest changes in fatty acid composition when grown in the presence of ethanol (Ingram et al. 1978). Studies by Noble et al. (1976) have demonstrated that ethanol produces changes in the levels of exposed sialic acid in cultured astroblast cells (a type of cell found in the central nervous system), which probably reflects changes in glycoprotein composition or organization within the membrane.

## ***Summary and Future Directions***

1. The rational development of methods for the prevention, recognition, and treatment of ethanol-related diseases requires a fundamental understanding of the basic mechanisms by which ethanol affects cellular function.
2. Ethanol affects all tissues of the body, and the cell membranes of these tissues are a primary site of its action. Ethanol interacts



with membranes to cause a small increase in overall membrane fluidity. The specific mechanisms by which ethanol interactions affect membrane processes are unknown, but the diversity of membrane lipids and proteins and the many cellular processes affected by ethanol indicate that the effects of ethanol are complex. More research is needed to determine the specific effects of ethanol on the complex organization of membranes and on specific membrane components. These studies should employ both native and model systems.

3. In many ways, ion flows associated with active transport are similar to those associated with neural function. Both of these processes are impaired by ethanol. Transport systems are particularly suited to biochemical investigations and should provide excellent models in future research to define the specific interactions of ethanol and the relationships between membrane composition and enzyme function.
4. Ethanol impairs neural function by interfering with complex neural processes that involve several membrane-associated events. Although research has eliminated many proposed mechanisms for this impairment, much more research is needed to define the specific actions of ethanol in central nervous system depression and local anesthesia. Care should be exercised to clearly delineate which biological characteristic is under consideration.
5. There is general agreement that alcohol tolerance and alcohol dependence result from changes in membrane organization and may involve changes in lipid composition. Various investigators have produced a considerable body of information comparing some aspects of lipid composition in normal and ethanol-tolerant animals. However, no comprehensive analysis of lipid and protein components is available. New research is needed to define in detail the alcohol-induced changes in the biochemical composition of synapses and other neural tissues.
6. Studies of tolerance and dependence and their molecular mechanisms are based primarily on correlations of changes. Considerable effort and ingenuity are needed to devise tests of these correlates and to establish possible mechanisms of action.
7. Lipid changes are thought to be involved in the acquisition of alcohol tolerance and dependence. However, the regulation of lipid composition is poorly understood even in normal tissues. Additional research is needed to define the regulation of fatty acid, phospholipid, and sterol composition in membranes and subsequently to define the mechanism by which ethanol induces changes.
8. The synthesis and excretion of proteins by cells, as well as cellular synthesis of some integral membrane receptors, is impaired by ethanol. The surface receptors are vital in the coordination of cellular functions including growth and differentiation. New research should be done to examine the effects of

- ethanol on the synthesis and processing of proteins at a molecular level. Ethanol-induced changes at this level could be involved in a wide variety of alcohol-associated diseases, from histological and anatomical changes in organs to the fetal alcohol syndrome.
9. All tissues are composed of a variety of cell types, each with specialized activities. This diversity confuses detailed biochemical analysis of ethanol effects. Although cells in culture often do not reflect all the properties they have in the living organism, cultured mammalian cells should be useful systems for examining specific effects of ethanol on fundamental cellular functions.
  10. Although simple microbial systems are vastly different from human tissues, the types of protein-lipid interactions that occur at a molecular level within cellular membranes are quite similar in the two systems. Microbial systems are uniquely advantageous for studying the fundamental relationships between structure and function in cell membranes and should provide useful information on the fundamental effects of ethanol on membrane components.

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## Chapter 2





# Alcohol and Protein Synthesis

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## Abstract

Alcohol results in alterations in cellular metabolism. Since the synthesis of protein requires the integration of total cellular metabolism, the effects of alcohol and its metabolite acetaldehyde on the synthesis of protein is a sensitive index of the acute and chronic effects of alcohol on cell function. However, not only is the mechanism whereby alcohol interferes with protein synthesis not fully understood, but the effects of alcohol and acetaldehyde differ depending on the organ. The liver synthesizes protein for use intracellularly as well as protein for secretion into the plasma. Exposure of the liver to alcohol results in an inhibitory effect on plasma protein synthesis due to a dismantling of the polysomes responsible for the synthesis of these proteins. This is partly reversible if the liver is from a well-nourished animal. Alcohol also inhibits intracellular protein synthesis, notably of those proteins used as enzymes within the mitochondria, organelles responsible for energy production within a cell. Impairment of function of these organelles may give rise to the liver pathology commonly observed in alcoholism. In contrast, the heart does not metabolize alcohol and does not appear to be affected by alcohol. However, contractile protein synthesis in the heart is seriously affected by acetaldehyde. The liver is the major site of acetaldehyde production and the heart is the first organ upstream from the liver, and it is suggested that cardiomyopathy occurs as a result of the acetaldehyde produced by the liver following the intake of alcohol. The brain likewise does not metabolize alcohol, but alcohol has a dual effect on brain protein synthesis, stimulating synthesis by one class of polysomes while inhibiting the other. Further studies are required to assess the significance of this effect on the tolerance to and physical dependence on alcohol.

## *Introduction*

All diseases, including alcoholism, are accompanied by some alteration in cellular nutrition that affects protein synthesis. A decrease in the synthesis of a protein molecule will disturb the delicate balance of reactions within a cell. Depending on which protein is involved, the effect could be minor and temporary or hazardous to the cell. And if

alterations in protein synthesis continue, enough cells may be involved to damage an organ or pose a threat to the organism itself.

This paper reviews current knowledge and controversies about the effects of alcohol on protein synthesis and analyzes the methods for studying these effects. Before discussing the effects of alcohol on protein synthesis, however, a brief review of the properties of proteins and the mechanism of protein synthesis is necessary to provide a background. Readers who are already familiar with these matters may skip the next two sections.

### *Properties of Proteins*

A protein is a polymer—a large molecule comprised of many fundamental subunits joined together by chemical bonds. Since proteins are made by living organisms, they belong to the special class of polymers called biopolymers. In proteins, the subunits are amino acids, of which there are 20 kinds. The amino acids are chemically joined together to make a chain. The link between adjacent amino acids in the protein chain is a chemical bond called the peptide bond.

The number of amino acids linked together in this way can vary widely, but the term protein is reserved for amino acid polymers that contain a large number of amino acids. Thus molecules in which two amino acids are linked together are called dipeptides; those in which three are linked together are called tripeptides; those containing 2 to 35 amino acids are called oligopeptides (*oligo*—meaning just a few); and those containing 25 to 100 amino acids are called polypeptides (*poly*—meaning many). Only when the polymer contains more than 100 amino acids is it called a protein.

The name “protein” comes from a Greek word meaning “that which is of prime importance.” Proteins are essential components of all living systems from the most elementary to the most complex. Living cells manufacture proteins to maintain their own integrity and to carry out specialized functions that are necessary for the well-being of the organism. The unique biological properties of each kind of protein are determined mainly by which of the 20 different kinds of amino acids are present; the sequence of these amino acids in the chain; and the attractions between amino acids that cause folds, coils, and bends in the chain, giving each kind of protein molecule its characteristic shape.

Although the number of specific protein types is very large, they have been reduced, in terms of biologic function, to eight major categories (Lehninger 1975). The functional categories are: structural proteins (found in connective tissue and muscle); storage proteins (e.g., ovalbumin in eggs, ferritin in liver); transport proteins (e.g., hemoglobin, serum albumin, lipoproteins); defense proteins (antibodies); hormone proteins (e.g., insulin); enzymes; and toxins (e.g., snake venoms, and byproducts of certain bacteria).

## *Protein Synthesis*

The production and maintenance of body proteins depend on dietary intake of their building blocks, including certain preformed, or "essential," amino acids that the cells cannot synthesize, as well as substances from which other amino acids can be made by the cells. The master "blueprint" for stringing these amino acids together in the correct sequence to make a specific protein is contained in a molecule of DNA (deoxyribonucleic acid) located in the cell's nucleus. The nucleus contains a specific DNA blueprint for each of the thousands of proteins that the cell makes.

Actual assembly of a protein molecule from its constituent amino acids occurs in the cytoplasm. A copy of the master blueprint in DNA is carried from the nucleus into the cytoplasm in the form of RNA (ribonucleic acid). This RNA molecule is a special type of RNA called messenger RNA (mRNA). The process by which the master blueprint is copied into mRNA—transcription—requires the action of an enzyme called RNA polymerase. The mRNA produced by transcription contains the code that determines the sequence of amino acids in the finished protein molecule.

Using this code to make a protein molecule requires a further step called translation. Translation occurs in ribosomes, which are complex structures composed of RNA and protein. The ribosome may be likened to the playback head of a tape recorder and the mRNA to the tape, except that in this case the "head" moves along the "tape." As the ribosome proceeds along the length of the mRNA, it "reads" the code and inserts the correct amino acid into a lengthening polypeptide chain that trails out behind it. When the ribosome reaches the end of the mRNA molecule it releases the completed protein molecule. This mechanism is used to make every protein in the body.

Actually, there are many ribosomes attached to a single mRNA molecule, one behind the other and all moving along its length, each reading the mRNA code and each attaching the correct amino acid at the correct point, building a protein molecule according to the blueprint. Thus one molecule of mRNA can be used for the translation of many protein molecules.

Some proteins consist of a single chain of amino acids, but others consist of two or more polypeptide chains held together by chemical bonds or other intermolecular forces. The subunit chains of these more complex proteins are designated by Greek letters (alpha chain, beta chain, etc.).

The translation process requires many enzymes—proteins that are specialized for catalyzing, or facilitating, chemical reactions in the body. During translation, they are needed to chemically activate amino acids by attaching them to specific carrier molecules called transfer RNA (tRNA). Other enzymes are needed to link the amino acids with peptide bonds, move the ribosome along the mRNA, and terminate translation.



The remarkable thing about protein synthesis is not its complexity but its fidelity. For example, in 24 hours the average person synthesizes so many molecules of the protein called serum albumin that if the molecules were laid end to end they would circle the equator nearly 45,000 times, yet each albumin molecule is so small that 1.7 million of them laid end to end would cover only an inch. With such a prodigious output, it is remarkable that errors in translation, i.e., insertion of the wrong amino acid at some point in the protein molecule, are so uncommon. The error rate in protein synthesis probably does not exceed 1 defective molecule in 10,000. Though the body's defense mechanism recognizes these defective molecules as "foreign" and destroys them, the loss of this small quantity of protein poses no threat.

Consistent insertion of the wrong amino acid, however, as in certain hereditary diseases, can have dire consequences. A dramatic example is sickle cell anemia, an inherited hemoglobin disorder in which the amino acid glutamic acid is always substituted by the amino acid valine at position 6 in the hemoglobin molecule's two beta polypeptide chains. This is a small error rate, involving only 2 amino acids out of 574, or 0.35 percent, yet this small error profoundly affects the properties of the hemoglobin molecule. The defect causes the red cells to lose their flat, disc-like shape at low oxygen tensions and take on a crescent or sickle shape. Sickled cells last only half as long as normal cells and tend to clump together, blocking small capillaries. (It is important to note that sickle cell anemia is not the result of faulty translation or transcription, for the DNA blueprint for sickle cell hemoglobin is as faithfully copied as the blueprint for any other protein. The error actually lies in the DNA blueprint itself; it is not coded to produce normal hemoglobin.)

## ***Alcohol and Protein Synthesis***

### *Methods of Studying Alcohol Effects on Protein Synthesis*

Ideally, metabolic experiments to test the effects of alcohol on protein synthesis should be carried out under completely normal conditions, but this is seldom possible.

When normal intact organisms are used in such studies, alcohol is administered by feeding, injection, or other methods and the tissues are then examined for any effects on protein synthesis. This seemingly simple procedure is beset with pitfalls. The direct effects of alcohol on a specific aspect of metabolism are often difficult to pinpoint when the whole animal is used. This is because alcohol affects many systems at the same time, including the gastrointestinal tract, heart, and central nervous system, and these systems function in an integrated manner. Thus a change induced in one system by alcohol is offset by adjustments in other systems, as the organism strives to maintain internal equilibrium.

Furthermore, the effects of alcohol in whole-animal studies vary according to the amount consumed, the time in which the amount is consumed, and the duration of continued consumption. To further complicate matters, the effects of alcohol in experimental animals depend on the route of administration, the animals' nutritional state, and their previous exposure to other noxious agents such as carbon tetrachloride. Finally, in long-term studies involving chronic exposure to alcohol, the direct effects of alcohol on an organ system can be confounded by its secondary effects on remote organ systems.

To get around many of these problems, investigators have turned to techniques where the tissues of interest are removed from the animal and studied in isolation. Such techniques are referred to as *in vitro* techniques (Latin for "in glass"), in contrast to *in vivo* techniques (Latin for "in life"). One such technique is organ perfusion. In this procedure the organ under study is removed from the animal with as little trauma as possible and kept under conditions that are as close as possible to those that are present in the animal. The organ is then perfused with the animal's own blood or with special solutions that fulfill the organ's physiological requirements. Alcohol can be added to the perfusing medium in order to test its effects on the organ. An advantage of this system is that it is removed from all secondary influences, such as those from hormones and the nervous system, that would be present in the intact animal. Another advantage is that the concentration of test substances in the perfusing medium can be carefully controlled. A major disadvantage is that many animals have to be sacrificed to establish a statistically valid baseline among control animals in order to provide a point of reference for results obtained from the experimental animals.

Another technique, lower on the level of biological organization, is the tissue slice. Thin slices of the organ are made and incubated in media under carefully controlled conditions. The advantage of this technique is that fewer experimental animals are required, since each organ serves as its own control; any effect by a test substance on the tissue slice can be referred to a tissue slice incubated in a medium without the test substance. A major disadvantage is that not all cells in the tissue slice receive adequate exposure to oxygen and to nutrients in the medium, and some of them die. For this reason, metabolic studies with tissue slices are not nearly as popular as they once were.

Still lower on the scale of biological organization are isolated organ cells. Use of such systems has gained wide popularity. The isolated cell system has the same advantage of tissue slice systems in that many experiments can be done on the same organ from one animal, thus eliminating interanimal differences. Isolated cells have another advantage over tissue slices in that all or nearly all of them remain alive during the experiment, and all are equally exposed to oxygen and the medium.

The lowest level of biological organization is the cell-free system, where cells are completely disrupted and the subcellular systems are isolated for study of their specific reactions.



All of these techniques—from whole-animal systems to subcellular systems—are used to study the effects of alcohol on protein synthesis, and useful metabolic information is obtainable with each of them. Each has its limitations, however. To achieve the best possible understanding of the integrated metabolism of the animal as a whole, data must be obtained at all these levels of biological organization and must be carefully correlated.

Most studies of the effects of alcohol on protein synthesis have used alcohol concentrations ranging from 0.23 percent to 0.46 percent. Alcohol's actions on cells can be separated into two distinct categories. One category includes the direct and indirect consequences of alcohol metabolism that are seen at concentrations about 0.04 percent. The other category includes the pharmacological effects that occur when alcohol concentrations are high—around 0.5 percent—and begin to affect the structural components of the cell. To provide a frame of reference for these figures, legal intoxication is often defined as a blood alcohol concentration over 0.1 percent. In New York State it is unlawful to drive a motor vehicle with a blood alcohol level above 0.05 percent.

### *Effects of Alcohol on Hepatic Protein Synthesis*

The metabolic effects of alcohol are restricted to organs that metabolize alcohol. Of these organs the preeminent one is the liver. The liver performs numerous diverse functions, including detoxification of metabolically-produced ammonia and many ingested compounds, formation of bile and excretion of bile salts (cholesterol metabolites), regulation of blood glucose levels, and synthesis of many plasma proteins including several blood clotting factors. The many functions of the liver require a vast number of enzymes, which are themselves proteins synthesized by the liver. In many ways, then, hepatic (i.e., liver) functioning depends on the maintenance of protein synthesis.

Because the liver synthesizes many of the plasma proteins, plasma protein synthesis has been used as an indicator of any effects of alcohol on protein synthesis. It has been shown that a concentration of alcohol equivalent to that reached in a person who has two or three martinis before lunch will cause a 50-60 percent decrease in the synthesis of serum albumin in isolated perfused rabbit or rat liver, or in the livers of intact rats (Jeejeebhoy et al. 1972; Kirsch et al. 1972; Rothschild et al. 1971).

Synthesis by the liver of proteins involved in blood clotting appears more resistant to the effects of alcohol. The synthesis of fibrinogen, the principal blood clotting protein, was not inhibited by alcohol in the concentrations used to demonstrate inhibition of albumin synthesis (Jeejeebhoy et al. 1972), and chronic alcohol feeding to rats for 45 days did not affect the synthesis of other proteins involved in the clotting process (Morland 1974c).

In the acute studies cited above, depressed protein synthesis was prevented by the addition of amino acids to the diet or to perfusing media.

The problem of secondary effects when working with intact animals was observed by Nadkarni (1974) who reported that orally administered alcohol inhibited plasma albumin synthesis within 1.5 hours in rats, whereas alcohol injected into the abdominal cavity did not inhibit the synthesis even though the blood alcohol level was three times higher. Nadkarni suggested that the high level of blood alcohol may have stimulated the release of thyroid and steroid hormones. Both groups of hormones stimulate albumin synthesis; thus they could have overcome the inhibitory effect of alcohol.

Experimentally, the synthesis of a plasma protein by the liver is determined by measuring the amount of the protein circulating in the blood. What is actually measured in this approach, however, is the net effect of two processes: synthesis of the protein in the liver cells, and subsequent secretion of the protein into the blood. There is evidence that the decreased levels of certain plasma proteins are partly due to decreased secretion. For example, experiments with rat liver slices have indicated that alcohol slows the liver's rate of secretion of glycoproteins (Sorrell and Tuma 1978; Tuma et al. 1980). Further evidence for decreased secretion is seen in studies showing that rats fed alcohol 4-8 weeks develop enlarged livers, and that some of this increase in liver mass is due to increased protein content. A small fraction of the retained protein are the serum proteins albumin and transferrin (Baraona et al. 1975, 1977). Inhibition of synthesis and/or secretion of plasma proteins must ultimately affect the internal equilibrium of the organism, but it does not explain how alcohol damages the liver.

With one exception, the synthetic mechanism is the same for proteins that are to be secreted and proteins that are to remain inside the cell. The exception: proteins destined for secretion (e.g., albumin) are synthesized by ribosome-mRNA complexes (polysomes) that are attached to a system of intracellular membranes called the endoplasmic reticulum, whereas proteins that will remain inside the cell (e.g., enzymes and structural proteins) are synthesized by unbound polysomes. Studies of polysomes after an acute exposure to alcohol indicated that alcohol caused a marked disruption of bound polysomes (Rothschild et al. 1971, 1974). The disruption apparently was the result of interference with the binding of the first or second ribosome to the mRNA since it could be reversed by adding spermine, a compound known to cause the disrupted polysomes to reaggregate (Oratz and Rothschild 1975; Oratz et al. 1975, 1976).

Alterations in hepatic intracellular protein synthesis would be expected to play an important role in the development of liver disease following exposure to alcohol. However, the reported results are equivocal and again point up the importance of the mode of administration and the model used. Intracellular hepatic protein synthesis, as

determined by radioactive amino acid incorporation, was decreased when rat liver slices (Perin et al. 1974) or isolated rat hepatocytes (Morland and Bessesen 1977) were incubated in an alcohol-enriched medium. On the other hand, no change in the synthesis was found when isolated rat liver was perfused with alcohol (Morland 1975). However, livers from animals chronically exposed to alcohol for 4-6 weeks showed significant reduction in hepatic protein synthesis (Morland and Sjetnan 1976b).

The importance of administration methods and alcohol doses was again demonstrated in studies of the effect of alcohol on specific intracellular hepatic enzymes. Livers from rats given an acute dose of alcohol by injection into the abdominal cavity were found to have elevated levels of the enzyme tryptophan oxygenase when compared to control animals (Sardesai and Provided 1972). However, tryptophan oxygenase activity is decreased when livers are perfused with alcohol or when rats are fed alcohol (Morland et al. 1972; Morland 1974a, b, c). Similar results were obtained in studies of ornithine decarboxylase, an enzyme necessary for growth and development of young cells. Here, too, chronic administration of alcohol resulted in decreased synthesis of this enzyme (Poso and Poso 1980).

Contradictory effects are also seen in studies of protein synthesis in cell-free systems derived from the livers of animals exposed acutely or chronically to alcohol. (The cell-free systems contain isolated polysomes and certain cellular factors that enable the polysomes to synthesize protein molecules. Protein synthesis is reflected by the rate at which radioactive amino acids in the medium are incorporated into protein.) Kuriyama and colleagues (1971) found that 3 hours after an acute alcohol exposure, protein synthesis in a cell-free system from liver was 47 percent of that in a cell-free system derived from an unexposed liver. However, if the animal was chronically exposed to alcohol for 14 days, protein synthesis in the system was not decreased but enhanced.

As mentioned above, there are two classes of polysomes, one bound to the endoplasmic reticulum and the other free; and the effects of chronic exposure to alcohol on the amino acid incorporating ability of these two classes of ribosomes are different. Alcohol decreases the synthetic capacity of bound polysomes but has little effect on the free polysomes (Khawaja and Lindholm 1978; Murty et al. 1980). This point will be referred to again later in the section dealing with the effect on brain protein synthesis when alcohol is chronically administered to animals and then abruptly withdrawn.

### *Effects of Alcohol on Hepatic Mitochondrial Protein Synthesis*

The mitochondria are the organelles in which the cell's respiration takes place. Mitochondrial respiration is the principal source of energy that enables cells to do the varieties of mechanical, electrical, chemical, and osmotic work that constitute the life processes of organisms. The



process is carried out by a superbly integrated complex of enzymes within the mitochondria. About 10 percent of these enzymes are made by the mitochondria's own protein-synthesizing mechanism; the other 90 percent are synthesized outside the mitochondria.

Chronic exposure to alcohol inhibits mitochondrial protein synthesis in various species. Mitochondria isolated from miniature swine that were allowed free access to alcohol for 3-6 weeks incorporated significantly less radioactive amino acid into mitochondrial protein than did mitochondria from control pigs (Burke et al. 1975). In comparable studies with rats fed alcohol in a balanced nutrient solution, mitochondrial protein synthesis was depressed by 33-50 percent (Bernstein and Penniall 1978; Hofmann and Hosein 1978). The exposure to alcohol not only decreased mitochondrial protein synthesis, it shortened the life of the mitochondrial proteins (Hofmann and Hosein 1978).

### *Effects of Alcohol on Hepatic Synthesis of Microsomal Proteins*

Microsomes are small fragments of the endoplasmic reticulum that are obtained when cells are disrupted and fractionated to yield subcellular components. The microsomal enzymes assist in the hydroxylation (a form of oxidation) of many different kinds of natural substances such as steroids and fatty acids, as well as various drugs such as phenobarbital, morphine, codeine, amphetamines, and many cancer-producing hydrocarbons.

Microsomal enzymes are inducible; that is, they increase in concentration in the liver of animals dosed with some of the above-mentioned drugs, particularly phenobarbital. Repeated alcohol ingestion also increases a variety of microsomal drug-detoxifying enzymes (Ishii et al. 1973a, b; Liu et al. 1975; Misra et al. 1971; Rubin and Lieber 1968; Rubin et al. 1970; Singlevitch and Barboriak 1971).

The induction of microsomal enzymes in response to alcohol partly explains the tolerance alcoholics have to various drugs, including resistance to phenobarbital, a member of the barbiturate class of sedatives. Among the enzymes induced by alcohol is phenobarbital hydroxylase, which catalyzes the detoxification of phenobarbital and other barbiturates. The increased level of the enzyme causes barbiturates to break down much faster in alcoholics, giving them greater tolerance to these drugs. The catch, however, is that chronic alcoholics are resistant to barbiturates only when sober; alcohol in the liver of a drunk alcoholic (or anyone else) depresses the activity of phenobarbital hydroxylase, causing dangerous sensitivity to the effect of barbiturates and a risk of fatal overdose.

Microsomal enzymes also participate indirectly in the increased rate of fatty acid and lipoprotein synthesis caused by administration of alcohol (Baraona and Lieber 1970). The result of greater synthesis of these substances is a condition called hyperlipemia, an increase in the amount of lipids (fats and fat-like substances) circulating in the blood.



The combination of lipids and protein to form lipoprotein is the body's way of making lipids water-soluble so that they can be transported through the body and be made available for metabolism in the tissues. Although hyperlipemia can occur without administration of alcohol (Baraona et al. 1973), the hyperlipemia associated with alcohol may be due to induction of a microsomal enzyme that catalyzes the conversion of fatty acids to derivatives called fatty acid esters. These in turn may induce the liver's production of lipoprotein.

### *Alcohol and Collagen Synthesis*

In its milder form, alcoholic liver disease is characterized by accumulation of fat in the liver. When the disease progresses to the point where liver cells die and the liver becomes inflamed, the condition is called alcoholic hepatitis. At this stage, scarring begins to occur in the liver and eventually begins to destroy the liver's normal architecture, leading to a condition called cirrhosis in which the liver is infiltrated with scar tissue. Scar tissue in the liver, as elsewhere, is composed principally of a protein called collagen.

Alcohol-induced accumulation of collagen—a protein—in the liver may seem inconsistent with the inhibitory effect of alcohol on hepatic protein synthesis discussed above. However, increased collagen deposition could also occur if alcohol decreased the rate of collagen breakdown, or if it both inhibited collagen breakdown and increased collagen synthesis at the same time. Several investigations have been made to determine which of these factors accounts for the collagen buildup in liver cirrhosis, or to see if both do.

One way to determine whether collagen synthesis is increased is by measuring the activity of an enzyme called proline hydroxylase. An increase in this enzyme's activity has been found to precede any increase in the final synthesis of collagen (Takeuchi and Prockop 1969; Uitto et al. 1970). Proline hydroxylase acts on a protein that is a precursor of collagen, converting about 40 percent of the precursor's proline amino acids to hydroxyproline. When the conversion process is complete, the protein is collagen. In other words, the enzyme puts the 'finishing touches' on newly synthesized collagen molecules. Because of this function, an increase in the activity of the enzyme is taken to mean that collagen synthesis is occurring.

Several investigators have used the technique. Feeding alcohol to rats and baboons resulted in increased collagen synthesis and deposition of collagen in liver before there was any sign of liver cell death or liver scarring (Patrick 1973) and was accompanied by increased proline hydroxylase activity (Feinman and Lieber 1972). Incubation of chick embryo tibia (shin bones) with straight alcohol and various alcoholic beverages also was shown to increase collagen synthesis. Interestingly, the effect occurred with scotch and brandy but not with gin (Walker and Shand 1972).

In human studies, alcohol evoked increased collagen synthesis in biopsied liver samples from subjects with alcoholic hepatitis or active cirrhosis. It was suggested that the stimulation of collagen synthesis by alcohol was provoked by the liver cell damage in these patients (Chen and Leevy 1975).

The importance of diet and alcohol on collagen synthesis was indicated by the data of Hakkinen et al. (1975). The authors reported that rats fed alcohol and a normal diet did indeed have increased collagen concentration in the liver after about 10 weeks. Similar results were obtained if the diet, devoid of alcohol, was high in fat and low in protein. Even so, the combination of high fat, low protein, and alcohol was the most effective in increasing collagen content in the liver.

Other studies have produced contrary evidence showing that increased collagen deposition is not due to increased collagen synthesis. Rats fed alcohol for 6 months had increased collagen deposits in their livers, but the increase was not the result of increased synthesis since it was not accompanied by increased proline hydroxylase activity or increased incorporation of radioactive proline into collagen (Mezey et al. 1977).

In another study to determine whether liver collagen increase was due to increased synthesis or decreased degradation, rats that were fed diets known to cause liver scarring were found to have increased liver collagen when alcohol was added to the diets. However, studies with radioactive proline incorporation into collagen indicated that the increase was due more to slower degradation of collagen than to inhibition of its synthesis (Henley et al. 1977). Nevertheless, the abnormal diets in this study make it difficult to interpret the role of alcohol in the mechanism of liver scarring.

Orrego and colleagues (1979) attempted to define the role of alcohol in liver scarring by operating on rats and passing a suture through a liver lobe. The lobe, with the suture in place, was returned to the abdominal cavity and the incision was closed. Some of the animals were then placed on diets containing alcohol, while others, the controls, were given the same diet without alcohol. After 10 days on these diets the animals receiving alcohol had 40 percent more liver collagen, concentrated around the suture. These findings are similar to those of Chen and Leevy (1975) in that alcohol can enhance the scarring induced by an outside agent (suture or cell damage). But here, too, it is not possible to distinguish between increased collagen synthesis and decreased collagen degradation as the mechanism responsible for these effects.

It is apparent from the foregoing discussions that alcohol inhibits protein synthesis. However, alcohol is converted in the liver to another toxic substance, acetaldehyde. This raises the question of which is truly the toxic substance as far as the liver is concerned—alcohol or acetaldehyde. To answer the question, studies were carried out with perfused rabbit livers, using perfusion media that contained either alcohol alone, acetaldehyde alone, alcohol plus 4-methyl pyrazole (a compound that blocks the conversion of alcohol to acetaldehyde), or

acetaldehyde plus disulfiram (a compound that blocks the breakdown of acetaldehyde). The results indicated that liver responses to alcohol and acetaldehyde differed according to whether the livers came from fed or fasted donors. It was not possible to attribute the toxic effects of acetaldehyde and alcohol to either agent alone (Oratz et al. 1978).

### *Effect of Alcohol on Protein Synthesis in the Brain*

Clinical observations point to decreased brain function in humans as a result of acute or chronic ingestion of alcohol. Most laboratory studies of alcohol's effect on the brain have been concerned with the effect of alcohol on energy metabolism, nerve transmission, and active transport (a process in which energy is used to transport substances in and out of cells). Unlike the liver, the brain does not metabolize alcohol to an appreciable extent.

Studies of the effect of alcohol on brain protein synthesis are not as clear-cut as those on liver. For convenience, the studies have been divided into three categories: acute alcohol administration, chronic alcohol administration, and withdrawal of alcohol after chronic administration.

#### Acute Administration of Alcohol

Results are unequivocal in acute administration studies. Alcohol injected into a mouse caused a 15 percent decrease in brain protein synthesis in 1.5 hours. By 3 hours, synthesis was down by 23 percent. Normal protein synthesis was resumed by 6 hours after the acute dose of alcohol. This response by the brain to alcohol was one-third that observed in the liver (Kuriyama et al. 1971).

Further studies on the course of effects after an acute dose indicated that depression of brain protein synthesis in the first 3 hours was due to damage in the protein-synthesizing mechanism in the polysomes (Lamar 1972). To see which type of cell was most affected by alcohol, brain tissue was examined after an acute dose. It was found that protein synthesis was inhibited in the glial cells but not in the nerve cells. (Glial cells are found in supporting tissues in the brain and other parts of the central nervous system. They do not carry nerve impulses.)

#### Chronic Alcohol Studies

Literature reports of chronic alcohol studies are contradictory. Kuriyama and colleagues (1971) reported that mice fed alcohol up to 14 days had enhanced brain protein synthesis. On the other hand, brain extracts from mice on alcohol for 10-46 days had impaired ability to incorporate amino acids into protein (Tewari and Noble 1971). Furthermore, fractions of these extracts inhibited protein synthesis when they were mixed with brain extracts from animals that had not been exposed to alcohol.



In studies where rats were given alcohol for 8 months, no difference was found between test and control animals in the rate of incorporation of amino acid into protein (Jarlstedt 1972). When the study was repeated, but with diets altered to provide the alcohol-imbibing rats with either a moderate or low protein intake, brain protein synthesis was decreased only in the animals receiving alcohol and a low protein diet (Jarlstedt and Hamberger 1972). Various alcoholic beverages were also tested for their effects on brain protein synthesis. In contrast to the experiments with chick tibia described in the section on alcohol and collagen synthesis, gin was the beverage with the strongest inhibitory effect on brain protein synthesis (Jarlstedt et al. 1978). Although these studies were unable to demonstrate any effect of chronic alcohol feeding, other studies indicated that 5 weeks of chronic alcohol intake reduces amino acid incorporation into cerebral proteins by 15 percent (Morland and Sjetnan 1976a).

### Withdrawal

As with chronic alcohol studies, the literature on withdrawal studies is contradictory. Rats on alcohol for 8 months incorporated more amino acid into brain protein after a 24-hour withdrawal from alcohol (Jarlstedt 1972). On the other hand, rats made physically dependent on alcohol had lower brain protein synthesis 24 hours after withdrawal, and brain protein synthesis did not return to normal until 7 days after withdrawal (Tewari et al. 1977).

Recent experiments (Tewari et al. 1978) have begun to clarify the situation somewhat. It appears that the discrepancy may be linked to the fact that brain tissue, like liver tissue, has two kinds of polysomes, each with a different response to alcohol. The population of polysomes in the brain is similar to that in the liver, in that there are polysomes that are free and those that are bound to the endoplasmic reticulum. As discussed earlier, bound polysomes in the liver usually make proteins that are to be secreted. The significance of bound polysomes in the brain, a nonsecretory organ, is not known. It is thought, however, that bound polysomes are more responsive to growth and development stimuli (Tata 1973).

To clarify the role of brain polysomes, studies were carried out with young rats fed a diet containing alcohol for 14 days. Free and bound brain polysomes were then isolated to study the incorporation of various amino acids into protein. For all amino acids studied, the free polysomes from the alcohol-fed rats incorporated more amino acids into protein than did those from a control population. In contrast, the ability of the membrane-bound polysomes to synthesize protein was greatly reduced (Khawaja et al. 1978). It was later found (Lindholm and Khawaja 1979) that the decreased protein synthesis by bound polysomes was due to damage of the endoplasmic reticulum by alcohol; when the membrane was removed from the preparations, the polysomes were able to show the stimulatory effect of alcohol.



Thus a possible explanation for the contradictory results reported in long-term chronic alcohol studies is that the studies were carried out with cell fractions that had different distributions of free and bound polysomes. Since alcohol stimulates protein synthesis in one kind of polysome and inhibits it in the other kind, either stimulation or inhibition might occur depending on the proportions of these two classes of polysomes in the cell fractions under study.

### *Effect of Alcohol on Cardiac Protein Synthesis*

Although much work has been done on alcohol's effects on blood pressure, heart performance, and blood flow through the coronary arteries, few studies have examined the effects of alcohol on protein synthesis in the heart.

One of the earliest of these studies was carried out with a perfused guinea pig heart (Schreiber et al. 1972). Perfusion with levels of alcohol that inhibited albumin synthesis in the liver did not alter amino acid incorporation into heart protein, but if the hearts were perfused with acetaldehyde—the metabolic product of alcohol—protein synthesis was reduced by half. Since this could have been due to stimulation of heart contraction by acetaldehyde, which can also affect protein synthesis, a second study was done using the isolated cell-free protein synthesizing system in order to eliminate any effects of heart contraction. Protein synthesis was again inhibited by acetaldehyde, indicating that acetaldehyde directly affects the heart's protein synthesizing mechanism. While alcohol itself had no effect on the cell-free system, acetaldehyde at concentrations seen in humans after moderate drinking inhibited protein synthesis 35-50 percent, depending on the dose (Schreiber et al. 1974).

That alcohol itself is not toxic to heart protein synthesis was further confirmed by the studies of Rawat (1979), which showed that administering an acute dose of alcohol to rats had no effect on amino acid incorporation by subcellular fractions of their hearts. On the other hand, feeding the animals alcohol for 4 weeks decreased the protein content of the hearts. Polysomes isolated from these hearts did not incorporate amino acids as well as controls, and experiments on systems isolated from these animals again confirmed the inhibitory effect of acetaldehyde on protein synthesis.

The loss of heart protein after chronic exposure to alcohol and the lack of any effect on protein synthesis by acute exposure to alcohol can be related to the production of acetaldehyde in the chronically exposed animal. Although acetaldehyde is not generated in the heart, it is generated in the liver. Blood leaving the liver carries acetaldehyde produced by hepatic alcohol metabolism, and immediately takes it to the heart where it can carry out its insidious activity. There is speculation that the same process might occur in humans.

*Consequences of Altered Protein Synthesis*

The health of the organism depends on proper functioning of organs. The proper functioning of an organ in turn depends on the proper functioning of its cells. And the proper functioning of a cell depends on its ability to maintain protein synthesis. We can now use information from the foregoing discussions to draw some conclusions, as well as some speculations, concerning the wider effects of alcohol's inhibition of protein synthesis in cells.

- Enzymes, which are proteins, play a vital role in metabolism by catalyzing many chemical reactions. Impaired protein synthesis resulting from alcohol abuse can result in a deficiency of enzymes needed in the production of substances vital to the cell's survival.
- A beating heart continually breaks down protein. Acetaldehyde inhibits heart protein synthesis. Continual exposure to acetaldehyde interferes with the replenishment of heart protein and can ultimately lead to protein deficiency and subsequent heart damage.
- The mitochondria are the cell's principal energy producers. They synthesize some of their own enzymes and incorporate other enzymes produced in the cytoplasm. The incorporation of the enzymes from the cytoplasm and their organization into the mitochondrial membrane requires the activity of certain enzymes produced by the mitochondria. If the decreased synthesis of mitochondrial enzymes that occurs when isolated mitochondria are exposed to alcohol also occurs in the living organism, it could affect the proper integration of cytoplasmic enzymes into the mitochondria. Whether an exaggeration of this sequence of events leads to the death of liver cells and cirrhosis of the liver remains to be established (Hofmann and Hosein 1978).
- Decreased protein synthesis in a cell can not only affect the cell, but can also affect a distant organ—or even a fetus, as seen in the following example. The synthesis of a protein hormone called rat chorionic mammatropin (rCM) in the placentas of pregnant rats was compared in rats fed a normal diet supplemented with alcohol and rats fed the same diet without alcohol. Alcohol lowered the capacity of the placenta to secrete rCM into the bloodstream, causing the mothers that consumed alcohol to have serum levels of rCM 50 percent lower than their nondrinking counterparts. Since the function of rCM is to raise the levels of glucose and amino acids in the maternal blood and to transfer those substances across the placenta in order to nourish the fetus, the reduced levels of the hormone resulted in impaired fetal growth (Wunderlich et al. 1979).

## ***Future Studies***

The problem with alcohol is that continued use impairs the ability of the organism to function. Past studies of alcohol have convincingly demonstrated its inhibitory effect on protein synthesis. Since it is recognized that complete abstinence from alcohol by the population is unrealistic, future studies should focus on the mechanism of this inhibitory effect and on ways to prevent it or reverse it.

The effects of alcohol in experimental animals depended on the dose, method of administration, and the nutritional status of the animals. Animal models should be developed that mimic human drinking habits. Unlike experimental animals, humans often ingest alcohol without food, or with an abnormal diet such as pretzels, peanuts, or canapes. The interrelationship between nutrition and alcoholic disease is not known and should be studied.

Society has finally begun to accept the reality that alcoholism is not a behavioral problem but a disease. Why do some people get the disease while others do not? Why can some people drink and then quit while others become addicted to alcohol? The problem in a nutshell is: How do we identify the people at high risk of getting this disease?

Addiction to alcohol is probably a result of a defect in the central nervous system. It is possible that alcohol, by altering protein synthesis in the central nervous system, alters the cell's response to its natural environment. Since dead nerve cells cannot be replaced, the cells of the central nervous system probably have evolved a high capacity for adaptation in order to survive. To survive in an alcoholic environment these cells probably adapt to it. Then, when alcohol is absent, the cells respond to the "foreign" environment by "forcing" the organism to supply them with alcohol. If the premise is accepted, basic research on the biochemistry of cell membranes should be encouraged. This is a difficult field of biochemistry, but biochemical techniques are improving, and in time the gaps of knowledge concerning membrane structure and function will be filled. (L. O. Ingram reviews the effects of alcohol on cellular membranes elsewhere in this monograph.)

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## Chapter 3





# Alcohol Effects on the Endocrine System

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## Abstract

This review focuses on the effects of alcohol on the endocrine system and the possible biological and pharmacological consequences of alcohol-induced alterations in hormonal status. It is clear from the literature that alcohol acutely and chronically depresses serum testosterone levels by a number of mechanisms, such as direct effects on the pituitary and testes and the degradation of the male sex hormone by the liver. It also appears that the reduced levels of serum testosterone found subsequent to acute and chronic alcohol administration may participate in some of the acute biological and behavioral responses to alcohol and perhaps the development of metabolic tolerance to it. Alcohol has also been found by most investigators to increase the output of adrenal hormones in humans and animals, but it is unclear at present whether this reflects a direct action of alcohol itself or the stress associated with its administration. Despite this uncertainty, however, some evidence has accumulated indicating that adrenal steroid hormones may play a role in the development of tolerance to and physical dependence upon alcohol. Alcohol also appears to decrease serum thyroxin and triiodothyronine levels after its acute or chronic administration in most species in which this has been examined. The consequences and significance of alterations in the hormones secreted by the thyroid are poorly understood, but recent evidence suggests that they may have some role in alcoholic hepatitis and cirrhosis of the liver. The effects of alcohol on many other endocrine systems (such as growth hormone, prolactin, vasopressin, and oxytocin) have been much less well characterized and future studies in this area are badly needed. However, it does appear that significant alterations in the circulating levels of these hormones do occur in most species. Furthermore, in the few studies currently available regarding the consequences of alcohol-induced alterations in these hormones, there is preliminary evidence that changes in these endocrines may contribute to the development of tolerance, physical dependence, and some of the biomedical consequences associated with alcoholism. The review indicates the need for many more carefully controlled studies of the effects of alcohol on the endocrine system and, particularly, on the ramifications of altered hormonal status with respect to the acute and chronic actions of the drug.

## ***Introduction***

The purpose of this review is to critically discuss the available literature regarding the possible involvement of alcohol-induced endocrine disturbances in the development of tolerance to and physical dependence upon alcohol and the biomedical consequences associated with its long-term use. At the outset it should be stated that there is a relative paucity of research in this area. Much of what we know is based on very recent studies. The recent burst of activity in this area stems from the realization of two important factors. First, alcohol exerts profound effects on virtually every endocrine system. Second, because of the pervasive influence of hormones in the cellular biochemistry of every organ in the body, drug-induced alterations in any endocrine system are likely to play an important role in the acute and particularly in the chronic actions of alcohol.

This review is divided into sections dealing with each endocrine system. Each section is divided into two subsections. The first subsection consists of an evaluation of the direct effects of acute and chronic alcohol administration in man and animals on the endocrine system in question. The second subsection reviews the possible involvement of alcohol-induced perturbations in this endocrine system in the development of the biomedical consequences associated with long-term use or in the maintenance of tolerance to or physical dependence on alcohol. The review is limited to endocrine systems for which there are sufficient data concerning the effects of alcohol or their possible involvement in the development of tolerance and physical dependence or in the biomedical aspects of chronic alcohol abuse. Suggestions for future research directions are provided in the final section.

## ***Conceptual and Methodological Issues Regarding Alcohol-Endocrine Interactions***

Studies of the effects of alcohol on endocrine systems have been hampered by a number of conceptual and methodological problems. This section provides a brief overview of these problems in several areas, including sex differences, pharmacological variables, endocrine variables, and chronic versus acute administration.

### ***Sex Differences***

Relatively few studies have been made on the effects of alcohol on neuroendocrine function in the female of any species. There are several reasons for this, such as the cyclicity of hormone secretion rates in the female, the fact that there are many more alcoholic males than there are females, and the habit of investigators to use male human

volunteers or animals rather than females. Consequently, there is a limited amount of data concerning the female in either humans or animals.

### *Pharmacological Variables*

There has been an unfortunate tendency in the past for many investigators to ignore basic pharmacological considerations in their investigations of drug-endocrine interactions. For example, many studies have examined the endocrine effects of a single dose of drug at one time interval after its injection. These studies are quite prevalent in humans, but there are also numerous examples in the animal literature as well. This unfortunate lack of attention to pharmacological details has led to misleading results and may partly explain some of the confusion in the literature, since it has been shown that alcohol exerts biphasic effects on many hormones as a function of both dose- and time-response considerations (Cicero and Badger 1977b; Cicero, Bernstein, and Badger 1978).

### *Endocrine Variables*

A number of variables associated with the determination of endocrine function are often ignored in alcohol-endocrine studies. As mentioned above, studies in the female have been avoided because of the cyclic nature of their hormone secretion rates. There are many such variations in the female, the most prominent of which are those associated with the menstrual or estrous cycle, but there are other episodic hormone secretory patterns as well (Cicero 1980c; Krieger 1975; Sassin et al. 1972; Weitzman et al. 1971; Yen et al. 1974). Although not nearly so well recognized by investigators, it appears that a good deal of temporal variation also occurs in the secretion of many hormones in the male, particularly testosterone and growth hormone (Baker et al. 1975; Bartke et al. 1973; Doering et al. 1975; Krieger 1975; Lacerda et al. 1973; Sassin et al. 1972; Weitzman et al. 1971; West et al. 1973). Thus, the effects of a drug on a specific endocrine system will depend on when a blood sample is obtained. As a result, single blood samples are simply not sufficient to completely characterize the endocrine effects of any drug. Unfortunately, many investigators have relied only on single blood samples, so their results are seriously compromised. In addition to the specific nature of hormone secretion rates, there are numerous other variables that might influence endocrine function apart from direct drug effects. These variables include the nutritional state of the subjects (animals or humans), the ingestion of drugs other than those under examination, for the stress associated with the experimental situation (Blake 1975; Dunn et al. 1972; Euker et al. 1975; Howland et al. 1974).

Another problem in many endocrine studies is that often only a single hormone is measured, and it is assumed that any change in its levels will reflect overall activity in the neuroendocrine system of which it is a



part. This is not always the case. Every endocrine system has complex negative and positive feedback controls (Fink 1979), such that changes in one aspect of the neuroendocrine axis profoundly affect activity in other portions of that axis. Consequently, multiple hormones should be measured in a single blood sample to obtain a definitive picture of the total impact of a drug on any neuroendocrine system. This has not always been done, making many results difficult to interpret.

### *Chronic vs. Acute Drug Administration*

Several important problems are encountered in chronic drug studies or when alcoholics are employed to study alcohol's effects on the endocrine system. First, from a conceptual viewpoint chronic administration of a drug provides a very poor vehicle to study drug-specific effects. It is difficult to control pharmacological variables like dose levels, drug-exposure periods, and the development of tolerance or physical dependence when chronic administration is used. Second, all endocrine systems display remarkable plasticity (Fink 1979) and by virtue of their compensatory feedback controls adjust their overall activity in response to alterations in any aspect of the system. Therefore, after a period of chronic drug exposure, one has no idea whether he is observing a direct effect of alcohol on a specific hormone or a secondary, compensatory alteration in that hormone. Third, when alcohol is given for very long periods of time, it may irreversibly damage a number of organs in the body, thus contaminating any studies of direct drug-induced alterations in endocrine function. Finally, the human alcoholic frequently has many problems not directly related to alcoholism. For example, multiple drug abuse is often a feature of the alcoholic, which makes studies of drug-specific effects difficult at best. Moreover, there are other problems such as psychiatric and medical difficulties (e.g., organ pathology) that cloud an interpretation of any endocrine data.

## ***Alcohol-Endocrine Interactions in the Hypothalamic-Pituitary-Gonadal Axis***

### *Direct Effects of Alcohol*

One general observation can be made about the effects of alcohol on the hypothalamic-pituitary-gonadal axis: in every species, alcohol appears to reduce serum testosterone levels significantly when acutely administered to the male; in comparison to controls, testosterone levels are markedly lower in alcoholics or animals chronically exposed to alcohol (Badr and Bartke 1974; Baker et al. 1976; Cicero and Badger 1977b; Cicero, Bell, and Badger 1980b; Cicero, Bell, Meyer, and Badger 1980; Cicero, Bernstein, and Badger 1978; Cicero, Meyer, and Bell 1978; Distiller et al. 1976; Dotson et al. 1975; Farmer and Fabre 1975;

Gordon and Southren 1977; Gordon et al. 1976, 1978; Lester and Van Thiel 1977; Marks and Wright 1977; Mendelson and Mello 1974; Mendelson, Ellingboe, Mello, and Kuehnle 1978; Mendelson, Mello, and Ellingboe 1978; Mendelson et al. 1977; Persky et al. 1977; Southren and Gordon 1970, 1976; Symons and Marks 1975; Van Thiel and Lester 1976; Van Thiel et al. 1975; Wright et al. 1976; Ylikahri, Huttunen, Harkonen, and Adlercreutz 1974).

Four mechanisms could account for a reduction in serum testosterone levels after acute or chronic alcohol administration. First, alcohol could enhance the metabolism of testosterone by the liver. Second, it could block the biosynthesis of the steroid at the level of the testes. Third, it could suppress the synthesis and/or release of luteinizing hormone (LH) from the pituitary and thereby inhibit LH-dependent testicular steroidogenesis. Finally, it could inhibit the release of LH-releasing hormone (LH-RH) from the hypothalamus, resulting in a series of secondary effects on the pituitary and testes. These possibilities are discussed below.

### Liver

It is well-documented that the clearance of testosterone is markedly enhanced relative to controls in chronic alcoholic humans or animals (Bode et al. 1978; Distiller et al. 1976; Gordon and Southren 1977; Gordon et al. 1978; Lester and Van Thiel 1977; Rubin et al. 1976; Southren and Gordon 1970, 1976). This appears to be due to induction of the enzymes responsible for the degradation of testosterone in the liver, primarily 5- $\alpha$ -reductases (Bode et al. 1978; Gordon et al. 1976; Rubin et al. 1976). Increases in these enzymes undoubtedly contribute to the reduced serum testosterone levels found in the alcoholic or animal chronically exposed to alcohol, but recent studies by Gordon and his colleagues (Gordon, Southren, and Lieber 1979; Gordon, Vittek, Ho, Rosenthal, Southren, and Lieber 1979) add some complexity to the issue. These investigators found that prolonged administration of alcohol to baboons (>1 year) or man decreased the activity of 5- $\alpha$ -reductases. They suggested that this may explain the observation that the metabolism of testosterone is often depressed in humans subjected to very prolonged alcohol consumption (Baker et al. 1976; Southren et al. 1973). Moreover, these investigators speculated that a reduced conversion of testosterone to dihydrotestosterone in the secondary sex organs (e.g., the prostate and seminal vesicles), resulting from decreased 5- $\alpha$ -reductase activity, could further exacerbate the effects of alcohol on testosterone-dependent systems.

Other alterations in the metabolic fate of testosterone after prolonged administration of alcohol in humans and animals have been demonstrated. For example, chronic alcohol administration has been associated with increases in circulating estrogens (Gordon et al. 1975; Gordon, Southren, Vittek, and Lieber 1979; Van Thiel et al. 1975), and this increase in plasma estrogen levels correlates with an increase in

hepatic aromatase activity (Gordon, Southren, Vittek, and Lieber 1979), an enzyme involved in converting androgens to estrogens. Moreover, it has been shown that there is an increased rate of conversion of testosterone and androstenedione to their respective estrogens in man (Baker et al. 1976; Gordon, Southren, and Lieber 1979; Gordon et al. 1975). Since estrogen administration (Gordon, Southren, and Lieber 1979) promotes signs of "feminization" (e.g., gynecomastia and testicular atrophy), it seems probable that increases in the formation of estrogens, coupled with decreases in serum testosterone levels, may play a significant role in the disturbances in reproductive endocrinology in the chronic alcoholic.

## Testes

A good deal of evidence suggests that alcohol exerts direct effects on the production of testosterone by the testes in the male of every species after both acute and chronic alcohol administration. In most studies involving acute alcohol administration serum testosterone levels are found to be depressed within 1 to 2 hours, reaching a maximum level of depression 3 to 5 hours after the administration of the drug. After this initial depressant phase testosterone levels return to normal or in some cases "rebound" 6 to 8 hours later when blood alcohol concentrations have declined to very low levels (Badr et al. 1977; Cicero and Badger 1977*b*; Cicero, Bell, and Badger 1980*b*; Cicero, Bell, Meyer, and Badger 1980; Cicero, Bernstein, and Badger 1978; Cicero, Meyer, and Bell 1978; Mendelson et al. 1977; Rowe et al. 1974; Ylikahri, Huttunen, Harkonen, Seuderling, Onikki, Kardnen, and Adlercreutz 1974). A biphasic effect of alcohol on serum testosterone levels has also been reported by Cicero and his colleagues (Cicero, Bell, and Badger 1980*b*; Cicero, Bernstein, and Badger 1978; Cicero, Meyer, and Bell 1978). Low doses of alcohol increased serum testosterone levels, whereas higher doses depressed them. These observations indicate the need to control for pharmacological variables and may partly account for a few reports in the literature that alcohol did not affect serum testosterone levels (Rowe et al. 1974; Toro et al. 1973).

The chronic effects of alcohol on serum testosterone levels in animals and humans have also been examined extensively. In agreement with the acute studies just described, most investigators have found that alcohol is a potent gonadal toxin in the male (Baker et al. 1976; Distiller et al. 1976; Gordon, Southren, and Lieber 1979; Lester and Van Thiel 1977; Symons and Marks 1975; Van Thiel and Lester 1976; Wright et al. 1976). Testosterone levels in serum are not only low in the chronic alcoholic or animal maintained on alcohol for a prolonged period of time, but it appears that with repeated and persistent usage alcohol ultimately damages the ultrastructural and biochemical architecture of the testes irreversibly (Baker et al. 1976; Lester and Van Thiel 1977; Symons and Marks 1975; Van Thiel and Lester 1976; Van Thiel et al. 1975; Wright et al. 1976).



The foregoing studies do not unequivocally establish that the locus of action of alcohol is at the testes. For example, it is equally plausible, based only on the data reviewed above, that alcohol might initially depress serum LH levels and that this results in decreased synthesis of testosterone.

One strong piece of evidence that a fall in serum testosterone levels does not necessarily depend on a fall in serum LH levels comes from observations in humans that LH levels do not necessarily covary in any systematic fashion with decreases in serum testosterone levels after acute or chronic alcohol administration. That is, decreases, increases, and no change in serum LH levels have been found after acute or chronic alcohol administration, even when serum testosterone levels are found to be markedly reduced (Baker et al. 1976; Gordon and Southren 1977; Gordon et al. 1976; Loosen and Prange 1977; Mendelson, Ellingboe, Mello, and Kuehnle 1978; Mendelson et al. 1977, 1980; Rowe et al. 1974; Simionescu et al. 1977; Toro et al. 1973; Van Thiel and Lester 1974, 1976, 1978; Van Thiel et al. 1974; Wright et al. 1975, 1976; Ylikahri et al. 1976, 1978). A second observation suggesting an independence of changes between serum LH and testosterone after acute alcohol treatment is that both seem to fall in essentially parallel fashion in the rodent, suggesting that these effects occur simultaneously rather than being causally linked (Cicero and Badger 1977*b*; Cicero, Bell, and Badger 1980*b*; Cicero, Bernstein, and Badger 1978; Cicero, Meyer, and Bell 1978). To assess this issue more directly, several groups of investigators have prevented an alcohol-induced fall in serum LH by giving rats subcutaneous injections of human chorionic gonadotropin (hCG) before injecting alcohol (Cicero, Meyer, and Bell 1978; Ellingboe and Varanelli 1979; Gordon, Southren, Vittek, and Lieber 1979). Testosterone levels still fell precipitously after acute alcohol administration, despite the fact that gonadotropin levels were far above those required to promote testicular steroidogenesis. These data seem to indicate unequivocally that alcohol exerts direct effects on the testes.

Several investigators have used *in vitro* preparations to characterize the effects of alcohol on testicular steroidogenesis more directly. Use of such preparations has shown that alcohol inhibits the basal or gonadotropin-stimulated production of testosterone by the testes in normal male rats (Badr et al. 1977; Cicero, Bell, and Badger 1980*b*; Cicero, Bell, Meyer, and Badger 1980; Cicero et al. 1979; Cobb et al. 1978, 1979, 1980; Dalterio et al. 1977; Ellingboe and Varanelli 1979). Moreover, Gordon, Southren, Vittek, and Lieber (1979) have shown that the testes from rodents chronically treated with alcohol responded very poorly to hCG-stimulation. It should be noted, however, that extremely high concentrations of alcohol have generally been required under *in vitro* conditions for significant inhibitions of testicular steroidogenesis, whereas very low doses of alcohol are required to inhibit testicular steroidogenesis *in vivo* (Cicero, Meyer, and Bell 1978; Ellingboe and Varanelli 1979; Gordon, Southren, Vittek, and Lieber 1979). Although



some of this difference might reflect inherently different sensitivity of *in vitro* versus *in vivo* preparations, it may be that the metabolism of alcohol, which occurs readily *in vivo* and minimally *in vitro* (Cicero, Bell, Meyer, and Badger 1980), may be responsible for the effects of alcohol on steroidogenesis.

The step in the biosynthetic pathway of testosterone that is inhibited by alcohol or acetaldehyde has been examined by two groups of investigators (Cicero and Bell 1980; Cicero, Bell, and Badger 1980b; Cicero et al. 1979; Gordon et al. 1980). Gordon et al. have provided evidence that alcohol blocks the conversion of pregnenolone to 17- $\alpha$ -hydroxyprogesterone. Cicero and his colleagues found that both alcohol and acetaldehyde significantly affected the conversion of androstenedione to testosterone. None of the other precursors of testosterone was affected by the two agents, including the conversion of pregnenolone to progesterone (the step implicated by Gordon and associates). Since the percent decrease in CPM incorporated into testosterone was completely offset by the increase in CPM incorporated into androstenedione, an inhibition of the conversion of androstenedione to testosterone appeared to completely account for alcohol's or acetaldehyde's effects on testicular steroidogenesis.

From the foregoing studies of Gordon and Cicero and their colleagues, it appears that alcohol and acetaldehyde directly affect the biosynthetic pathway for testosterone in the testes by two mechanisms. Both compounds directly affect the conversion of androstenedione to testosterone (*in vitro*), and this effect may be compounded by a reduction in the conversion of progesterone to 17- $\alpha$ -hydroxyprogesterone *in vivo*.

### Hypothalamic-pituitary-LH axis

Although the studies described in the preceding section seem to indicate that the inhibitory effects of alcohol on serum testosterone levels can be attributed exclusively to an action at the level of the testes, it is equally clear from a variety of studies that alcohol significantly affects the hypothalamic-pituitary-LH axis.

Several investigators have demonstrated that acute injections of alcohol significantly depress serum LH levels in rats (Cicero and Badger 1977a, b; Chapin et al. 1980; Cicero, Bell, and Badger 1980b; Cicero, Bernstein, and Badger 1978). Chronic alcohol administration has also been found to depress serum LH levels in rodents (Cicero and Badger 1977b; Cicero, Bell, and Badger 1980b; Symons and Marks 1975; Wright 1978). The situation in humans is not as clear. Increases, decreases, and frequently no change in serum LH levels have been found after acute or chronic administration of alcohol to humans (Baker et al. 1976; Gordon and Southren 1977; Gordon et al. 1976; Loosen and Prange 1977; Mendelson, Ellingboe, Mello, and Kuehnle 1978; Mendelson et al. 1977, 1980; Rowe et al. 1974; Simionescu et al. 1977; Toro et al. 1973; Van Thiel and Lester 1974, 1976, 1978; Van Thiel et al. 1974;

Wright et al. 1975, 1976; Ylikahri et al. 1976, 1978). Although these data could initially be interpreted to mean that alcohol has no impact on the hypothalamic-pituitary-LH axis, at least in humans, these results in fact argue for a strong effect on the central aspect of the hypothalamic-pituitary-LH axis. It is well established that the hypothalamic-pituitary-LH axis is continuously inhibited by testosterone (Damassa et al. 1976; Davidson 1969; Fink 1979). When the axis is relieved of this negative feedback control, serum LH levels rise 10-fold to 20-fold with respect to controls. Since serum LH levels were only modestly changed in all of these human studies, even though serum testosterone levels were markedly reduced, it appears that the hypothalamic-pituitary-LH axis must be significantly inhibited by alcohol. To directly assess this strong inference, the effects of alcohol on the castration-induced rise in serum LH levels in the male rat have been examined by several investigators (Chapin et al. 1980; Cicero and Badger 1977a; Cicero, Bell, and Badger 1980b; Cicero, Bernstein, and Badger 1978). In these studies alcohol markedly suppressed the increase in serum LH following castration, demonstrating unequivocally that alcohol affects the hypothalamic-pituitary-LH axis very substantially.

The bulk of currently available evidence suggests that alcohol exerts its effects on the hypothalamic-pituitary axis by acting on the hypothalamus. It has been found, for example, that acute or chronic alcohol administration does not reduce the rise in serum LH produced by systemically administered LH-RH (luteinizing hormone releasing hormone) in rats and humans (Baker et al. 1976; Chapin et al. 1980; Cicero, Bell, and Badger 1980b; Cicero, Bernstein, and Badger 1978; Cicero, Meyer, and Bell 1978; Leppaluoto et al. 1975; Symons and Marks 1975). Similarly, the effects of LH-RH on the release of LH by the anterior pituitary *in vitro* are not attenuated in the presence of relatively high concentrations of alcohol (Cicero, Bell, and Badger 1980b; Cicero, Bernstein, and Badger 1978; Cicero, Meyer, and Bell 1978). Furthermore, it has also been observed that if one uses alcohol to block the rise in serum LH induced by castration and then administers LH-RH, LH levels return promptly to those that existed before alcohol treatment (Chapin et al. 1980; Cicero, Bernstein, and Badger 1978; Cicero, Meyer, and Bell 1978). These data indicate that LH-RH can overcome alcohol's blockade of the hypothalamic-pituitary-LH axis, and indicate further that alcohol must exert its effects at a suprasellar site within this axis. However, Van Thiel and his associates (1974) have reported that the response to LH-RH provocation in chronic alcoholics was impaired in some cases, and Baker et al. (1976) also found that a small percentage of alcoholics responded poorly to LH-RH stimulation. It is not clear why these investigators found a pituitary effect of alcohol in some alcoholics, whereas other investigators did not (see above), but perhaps the chronicity of exposure or other intervening variables (e.g., nutrition, alteration in other endocrine systems) may explain these discordant findings. Nevertheless, it appears that alcohol can directly alter hypothalamic function (a view not seriously disputed by any investiga-

tor)—apart from whether or not it has any effects on the pituitary. The most likely mechanism by which alcohol affects the hypothalamus is by inhibiting release of LH-RH, but this has not been unequivocally established at the present time.

From the foregoing review of the effects of alcohol on the liver, testes, and hypothalamic-pituitary-LH axis it is apparent that alcohol exerts multiple effects on the hypothalamic-pituitary-gonadal axis. It is a potent inhibitor of testicular steroidogenesis. It significantly affects the metabolism and metabolic fate of androgens. And it significantly inhibits the synthesis and secretion of LH by the hypothalamic-pituitary-LH axis, presumably by acting on the hypothalamus. The combined effect of these multiple insults is a pronounced impairment of reproductive endocrinology and physiology in the male.

It is not known how extensively alcohol influences the function of the hypothalamic-pituitary-gonadal axis in females, since there are relatively few available studies to shed any light on the issue. It is known that alcohol appears to disrupt the menstrual cycle in humans and estrous cycle in rodents (Aron et al. 1965; Cranston 1958; Kieffer and Ketchel 1970; Luukkainen et al. 1967) and appears to be a significant gonadal (ovarian) toxin (Van Thiel et al. 1977), but few systematic studies have been done.

### *Consequences of Alcohol-Induced Alterations in the Hypothalamic-Pituitary-Gonadal Axis*

The ramifications of acute alcohol-induced changes in serum testosterone levels have received relatively little attention. Recently, however, several investigators have speculated about the significance of such changes with respect to the behavioral pharmacology of alcohol (Mendelson and Mello 1974, 1979; Mendelson, Mello, and Ellingboe 1978; Mendelson et al. 1977; Persky et al. 1977). Briefly, it has been hypothesized that changes in serum testosterone and LH levels after acute alcohol ingestion in human males may partly account for alterations in affective state and sexual behavior. Mendelson and colleagues have proposed that the decreased testosterone they observed in normal volunteers after acute ingestion of alcohol may lead to impaired sexual performance, while the concomitant increase in LH these investigators (but not others—see above) found after acute alcohol administration enhances sexual desire—thus providing an endocrine basis for the old Shakespearean adage concerning the effects of alcohol on sexual behavior.

Although these are intriguing possibilities, it should be noted that there is significant controversy regarding a correlation between testosterone levels and sexual performance, particularly with respect to acute alterations in testosterone levels (Bancroft 1978). Indeed, castrated male humans display normal sexual performance (i.e., maintenance of erections, ejaculation, etc.) for very long periods of time following complete removal of testosterone by means of orchiectomy (Sturup



1968). Since alcohol decreases testosterone levels only modestly when compared to castration, it seems difficult to maintain that these changes in circulating testosterone levels would have much significance in terms of sexual performance. Moreover, the traditional view that testosterone exerts long-term genomic influences, as opposed to acute short-term effects, also seems to argue against this possibility (McEwen et al. 1978). Finally, it should be noted that there is at present no established role in the human for LH as a mediator of sexual appetite or drive, although there has been some recent speculation that this may be possible (LaFerla et al. 1978). While these considerations tend to cast some doubt on the hypothesis that acute alterations in testosterone significantly affect sexual behavior, it should be noted that several investigators have recently reported that sex steroids exert electrophysiological effects within seconds after their iontophoretic application and that other hormones secreted by the hypothalamic-pituitary-LH axis elicit immediate effects in brain (Guillemin 1978; McEwen et al. 1978). Thus, on the basis of traditional views concerning the central nervous system actions of testosterone and other hypothalamic-pituitary-gonadal hormones, it would be unwise to dismiss these speculations.

Mendelson and others (Mendelson and Mello 1974, 1979; Mendelson, Mello, and Ellingboe 1978; Mendelson et al. 1977; Persky et al. 1977) have also postulated that changes in aggressive state following acute alcohol administration may be related to alterations in the secretion of testosterone and/or LH. These investigators have found that serum testosterone levels either did not correlate (Persky et al. 1977) or were inversely correlated (Mendelson and Mello 1974, 1979; Mendelson, Mello, and Ellingboe 1978; Mendelson et al. 1977) with self-reported aggression in normal human volunteers after acute alcohol administration. On the other hand, there appeared to be an excellent positive correlation between alcohol-induced increases in serum LH levels and aggressiveness—at least in the studies of Mendelson and his colleagues. On the basis of these observations they concluded that the frequently observed increase in aggression during alcohol intoxication in at least some individuals may be related to enhanced levels of LH.

Although these are interesting observations, it should be noted that at present there is no evidence to indicate that LH might be involved in passive-aggressive behavior in humans or animals. Moreover, the inverse correlation between serum testosterone levels and aggression seems somewhat surprising in view of the common assumption that the two may be positively linked (i.e., high testosterone levels are associated with aggression, whereas low testosterone levels are linked to more passive behavior). However, it should be noted that while some evidence suggests a causal relationship between testosterone levels and aggression, hostility, and criminal behavior in humans and animals, there is significant controversy regarding this point (Doering et al. 1974; Meyer-Bahlburg et al. 1974; Persky et al. 1971). Thus, the observation that self-reported aggression following acute alcohol administration does not appear to correlate with changes in serum testosterone levels



may not be too surprising. The conclusion, however, that increased LH levels may therefore be responsible for alcohol-induced alterations in passive-aggressive behavior must be considered as speculative at this point. More definitive studies are obviously required to establish the validity of this hypothesis. Nevertheless, the studies of Mendelson and his colleagues seem to be an encouraging first step in elucidating the role of changes in endocrine state in the behavioral pharmacology of alcohol.

Alcohol-induced reductions in serum testosterone levels have also been implicated in the development of metabolic tolerance to alcohol. Israel, Khanna, Orrego, Rachamin, Wahid, Britton, MacDonald, and Kalant (1979), Rachamin et al. (1980), and subsequently Cicero, Bernard, and Newman (1980), have reported that castration resulted in markedly enhanced levels of alcohol dehydrogenase in the liver and a corresponding increase in the clearance of alcohol. This effect occurred rapidly after castration and essentially reached a maximum within 2 to 3 days (Cicero, Bernard, and Newman 1980). Moreover, daily injections of testosterone readily reversed the effect, reducing alcohol dehydrogenase levels and lowering the clearance rate of alcohol. Since alcohol is known to markedly suppress serum testosterone levels, both acutely and chronically, both groups of investigators speculated that chronic alcohol administration might be equivalent to "chemical" castration. Some support for this hypothesis has recently been provided by Israel and colleagues mentioned above (1979). They reported that metabolic tolerance to alcohol could not be produced in castrated animals, whereas a significant increase in alcohol dehydrogenase and alcohol metabolism occurred in sham-operated animals after a period of chronic alcohol administration. These data were interpreted as supporting the notion that testosterone (which was absent in the castrate) was required to induce metabolic tolerance to alcohol.

The possible involvement of testosterone in the control of alcohol dehydrogenase leads to several interesting predictions regarding cross-tolerance between alcohol and other sedative-hypnotic drugs. It is well established that many drugs with which cross-tolerance with alcohol has been demonstrated also depress serum testosterone levels in males in several species. For example, narcotics and barbiturates are potent inhibitors of testosterone (Cicero 1977, 1979; Cicero and Badger 1977a; Cicero, Meyer, Bell, and Koch 1976; Cicero, Wilcox, Bell, and Meyer 1976; Cicero et al. 1977; Mendelson et al. 1975; Mirin et al. 1976), and there is good evidence of cross-tolerance between these drugs and alcohol. Cicero, Bernard, and Newman (1980) have examined whether chronic treatment with morphine increases alcohol dehydrogenase and alcohol clearance. In agreement with the previous research cited above, these investigators found that chronic morphine administration decreased testosterone levels by nearly 90 percent when compared to saline-injected controls. Associated with this significant reduction in serum testosterone levels, Cicero, Bernard, and Newman (1980) found that morphine produced a pronounced (85 percent)

increase in liver alcohol dehydrogenase activity that was completely reversed by daily injections of testosterone. The effects of chronic morphine administration on the disappearance of alcohol from the blood were also examined, and it was found that morphine markedly enhanced the clearance of alcohol. This effect was also reversed by testosterone.

The results of Cicero, Bernard, and Newman (1980) thus indicate that chronic morphine administration produces a marked metabolic tolerance to alcohol in the male rat which appears to be mediated by a depletion of serum testosterone levels. These results lend support to the hypothesis that liver alcohol dehydrogenase is under the control of testosterone and, furthermore, suggest that the testosterone-depleting effects of many abused substances may be an important biochemical mechanism mediating cross-tolerance between them.

There are essentially no data available on the role of alcohol-induced changes in the secretion of LH-RH or LH in the acute or chronic effects of alcohol (apart from the observations of Mendelson and coworkers referred to above). However, it is becoming increasingly clear that a number of steroids, pituitary hormones, and hypothalamic releasing factors have many actions in brain besides those normally ascribed to them (Gispen et al. 1977; Nemeroff et al. 1979; Plotnikoff and Kastin 1977; Ríghter and Crabbe 1979), and projections of cells containing hypothalamic releasing factors can be found in many diverse areas of brain (Elde and Hokfelt 1979; Jackson 1978; Swanson 1977). These newly discovered anatomical connections and the demonstration that hypothalamic releasing factors and other pituitary and target organ hormones have significant biochemical and physiological activities suggest a prominent role in brain function beyond their endocrine-related actions. There are no conclusive studies in which the effects of LH-RH, LH, or testosterone have been examined with respect to mediating the acute and chronic actions of alcohol on the brain, but in view of these recent developments such studies should be assigned high priority.

## ***Alcohol-Endocrine Interactions in the Hypothalamic-Pituitary-Adrenal Axis***

### ***Direct Effects of Alcohol***

Acute alcohol administration at appropriate doses elevates corticosterone levels in animals (Czaja and Kalant 1961; Ellis 1962, 1965, 1966; Forbes and Duncan 1951; Kakihana 1977; Kalant 1975; Noble 1971; Pohorecky et al. 1978; Smith 1951; Suzuki et al. 1972). Alcohol also acutely elevates cortisol levels in normal human volunteers (Bellet, Roman, Decastro, and Herrera 1970; Fazekas 1966; Jenkins and Connolly 1968; Merry and Marks 1969), but this has not been observed in all studies (Kissin et al. 1960; Mendelson and Stein 1966; Perman

1960; Wright 1978). The reasons for the latter discrepancies are not entirely clear, but they may be related to dose-response problems, which will be dealt with in depth below.

In general, it appears that after very high, intoxicating doses of alcohol in both animals and humans, serum corticosterone or cortisol, respectively, are elevated. With respect to chronic effects of alcohol on the hypothalamic-pituitary-adrenal axis in alcoholics, many groups have shown persistent elevations in cortisol and corticosterone after acute challenges with alcohol once a critical blood level is achieved or during the drinking phase (Crossland and Ratcliffe 1968; Forbes and Duncan 1953; Kakihana and Moore 1976; Kakihana et al. 1971; Kissin et al. 1960; Margraf et al. 1967; Marks and Wright 1977; Mendelson and Stein 1966; Mendelson et al. 1971; Merry and Marks 1969, 1972; Noble et al. 1971; Stokes 1973; Tabakoff et al. 1978; Wright 1978). Moreover, although tolerance has been found to develop to the effects of alcohol on the hypothalamic-pituitary-adrenal axis in some studies (Crossland and Ratcliffe 1968; Kakihana et al. 1971; Noble et al. 1971), most investigators have failed to find this (Ellis 1966; Mendelson and Stein 1966; Pohorecky et al. 1978; Stokes 1973; Tabakoff et al. 1978; Wright 1978).

Basal levels of cortisol in alcoholics have generally been found elevated in subjects who are still drinking (see references above), whereas they appear to be normal in abstinent alcoholics (Mendelson and Stein 1966; Mendelson et al. 1971; Stokes 1973). The effects of acute challenges with alcohol in abstinent alcoholics have also been examined, but conflicting results have been obtained. For example, Merry and Marks (1969) administered alcohol to acutely withdrawn alcoholics and found *depressed* plasma cortisol levels instead of the higher levels normally observed after acute administration in normals or alcoholics (see above). On the other hand, two groups have observed that acute alcohol administration to abstinent alcoholics produced increases in cortisol levels comparable to those found in normal subjects or drinking alcoholics (Mendelson et al. 1971; Merry and Marks 1972; Stokes 1973). At present it is unclear what accounts for these differences in results obtained with abstinent alcoholics.

Alcohol does not appear to act directly on the adrenals to enhance the secretion of steroids. Instead the locus of action seems to be on the hypothalamic-pituitary axis, based on the following observations: (a) pituitary ACTH levels were found to be depleted after acute alcohol treatment in rodents (Noble 1971; Noble et al. 1971), which appeared to correlate with increased corticosterone release; (b) alcohol has been found ineffective in promoting the release of corticosterone in hypophysectomized animals, indicating that an intact pituitary is necessary for an effect to be observed (Czaja and Kalant 1961; Ellis 1966; Forbes and Duncan 1951, 1953; Smith 1951); and (c) in humans with pituitary tumors in which there is clinical evidence of impaired ACTH release, alcohol does not lower cortisol levels (Jenkins and Connolly 1968).



While these three lines of evidence indicate that alcohol lowers serum corticosterone or cortisol by an action on the hypothalamic-pituitary axis, rather than the adrenals, measurements of the hypothalamic tissue content of CRF or the release of CRF into the hypophysis-portal or peripheral circulation have not been feasible since this releasing factor has thus far not been isolated or identified. Thus, it is impossible to state unequivocally at this time whether alcohol's effects are exerted at the level of the hypothalamus or pituitary.

A cautionary note should be made regarding the effects of alcohol or any drug on the hypothalamic-pituitary-adrenal axis: it is extremely difficult to state in any study of drug-induced changes in this axis whether one is observing a direct effect of the drug as such or a secondary consequence of the stress associated with acute or chronic drug treatment. In the case of alcohol, unfortunately, a very strong case can be made that its effects upon the hypothalamic-pituitary-adrenal axis are due exclusively to the stress associated with its administration. This conclusion is based on the observation that levels of corticosterone in rodents and cortisol in humans appear to be elevated only by extremely high, intoxicating doses of alcohol, not by low to moderate doses (Czaja and Kalant 1961; Jenkins and Connolly 1968; Kalant 1975; Kalant et al. 1963; Kissin et al. 1960; Mendelson and Stein 1966; Mendelson et al. 1971; Merry and Marks 1972; Stokes 1973). Although a good dose-response relationship was reported in the dog (Ellis 1962, 1965, 1966) and human (Jenkins and Connolly 1968), in most studies in humans or other animals a release of cortisol or corticosterone seems to occur in an all-or-none fashion once an intoxicating blood level of alcohol is achieved, and there is no apparent correlation between blood alcohol levels and corticosterone release (Czaja and Kalant 1961; Doering et al. 1975; Fazekas 1966; Jenkins and Connolly 1968; Kalant 1975; Kalant et al. 1963; Kissin et al. 1960; Mendelson and Stein 1966; Mendelson et al. 1971; Merry and Marks 1972; Stokes 1973). This lack of an appropriate dose-response curve may help explain a number of the discrepancies in the human and animal literature. It has also been found that the route of administration of alcohol and how fast the peak blood alcohol levels are attained determine whether an adrenal response occurs at all after acute alcohol administration (Gordon and Southren 1977; Kalant 1975; Kalant et al. 1963). If alcohol were exerting a drug-specific effect on this axis, a good dose-response relationship would be expected, and it is very difficult to imagine that the rate of onset of peak blood alcohol levels or the route of administration would be important variables if stress were not involved in some way. Until these issues are resolved, it is very difficult to conclude anything with respect to the specific effects of alcohol on the hypothalamic-pituitary-adrenal axis.



*Consequences of Alcohol-Induced Alterations in Hypothalamic-Pituitary-Adrenal Activation*

The consequences of acute alterations in corticosterone or cortisol production induced by acute alcohol administration in animals or humans, respectively, are poorly understood. However, Kakihana (1977) and Swanberg et al. (1979) have found that there is a substantial difference in two highly selected inbred strains of mice, the so-called long-sleep (LS) and short-sleep (SS) mice (Heston et al. 1974), in terms of acute corticosterone response to ethanol. In LS males the release of corticosterone after acute alcohol administration was much greater than similarly treated SS males or LS and SS females. This difference in adrenal activation produced by alcohol seems to parallel the genetically determined, enhanced sensitivity of LS mice to all effects of alcohol. However, a causal relationship between corticosterone release and other differences in the response to alcohol in these animals could not be unequivocally established (Kakihana 1977; Swanberg et al. 1979). Furthermore, while these data could be interpreted to indicate that alcohol specifically affects the hypothalamic-pituitary-adrenal axis (as opposed to a general, nonspecific stress effect), it is not clear that LS mice simply do not respond to alcohol by becoming more stressed by its administration. This issue is very difficult to resolve, however, and these results suggest at the very least that alcohol-adrenal interactions should not be ignored and may have important implications.

The development of alcohol tolerance and physical dependence appears to involve the hypothalamic-pituitary-adrenal axis. Sze and colleagues (Sze 1977; Sze et al. 1974) have demonstrated in both rats and mice that adrenalectomy markedly decreased the severity of the alcohol withdrawal reaction. These studies can be criticized on a variety of methodological grounds, however, since blood alcohol concentrations were not determined during the course of intoxication, and the possibility that adrenalectomy simply caused a diffuse response, which incidentally included a diminution of withdrawal behavior, was not considered or controlled in any way. Nevertheless, these results do provide a framework within which to begin to examine the possibility that the hypothalamic-pituitary-adrenal axis may mediate some of the chronic effects of ethanol.

In somewhat better controlled studies Kakihana (1977) has shown that mice with very high serum corticosterone levels had much more severe withdrawal seizures than did mice with low corticosterone levels. This study seems to corroborate the results of Sze et al. (Sze 1977; Sze et al. 1974) and suggests that the basal level of activity of the hypothalamic-pituitary-adrenal axis partly determines the chronic effects of ethanol on the central nervous system.

Several groups of investigators have also found significant interactions between the hypothalamic-pituitary-adrenal axis and the development of tolerance. For example, Sze (1975) reported that adrenalectomy abolished the increase in liver alcohol dehydrogenase resulting

from chronic alcohol administration in mice and suggested that enhanced activity in the hypothalamic-pituitary-adrenal axis played a "permissive role" in the development of metabolic tolerance to alcohol. In addition, two groups of workers have examined whether alcohol-induced alterations in the hypothalamic-pituitary-adrenal axis participate in the development of "functional" tolerance to alcohol. Tabakoff and Yanai (1979) found that treating rats with cortoloxone, a corticosterone antagonist, attenuated the development of tolerance following chronic maintenance on alcohol-containing liquid diets. Similarly, Wood (1977) found that chronic treatment with dexamethasone—a corticosterone-like compound—accelerated the development of tolerance and also counteracted the acute effects of alcohol to some extent. These three reports seem to provide good evidence that alterations in hypothalamic-pituitary-adrenal activity may play some role in the acute actions of alcohol and the development of metabolic and functional tolerance.

## ***Alcohol-Endocrine Interactions in the Hypothalamic-Pituitary-Thyroid Axis***

### ***Direct Effects of Alcohol***

The effects of alcohol on the thyroid gland have been investigated longer than for any other neuroendocrine axis. The reasons for this interest undoubtedly stem from the observations of Richter (1956, 1957) that thyroid extracts decreased preference for alcohol in male rats, whereas a decrease in the activity of the thyroid resulted in a marked increase in alcohol intake. Although these observations have been replicated by some (Hillborn 1971) but not all workers (Prieto et al. 1958), these reports stimulated interest in the possible involvement of the hypothalamic-pituitary-thyroid axis in the acute and chronic effects of alcohol.

The most consistent effect of alcohol on thyroid function is to decrease serum thyroxine levels (T4) modestly and serum triiodothyronine (T3) levels markedly (Augustine 1967; Bleecker et al. 1969; Chopra et al. 1974; Green et al. 1977; Israel, Walfish, Orrego, Blake, and Kalant 1979; Israel et al. 1973; Murdock 1967; Nomura et al. 1975; Orrego et al. 1979; Ramakrishnan et al. 1976; Stokes 1971). This effect has been observed after acute alcohol administration but is most pronounced in chronic alcoholics, particularly those with alcoholic hepatitis or cirrhosis (Augustine 1967; Bleecker et al. 1969; Chopra et al. 1974; Green et al. 1977; Israel, Walfish, Orrego, Blake, and Kalant 1979; Israel et al. 1973; Murdock 1967; Nomura et al. 1975; Orrego et al. 1979; Ramakrishnan et al. 1976; Stokes 1971). It appears, however, that the very low concentration of T3 in the serum of alcoholics and perhaps normals after acute alcohol administration does not reflect a direct action on the thyroid, since T4 levels and serum TSH levels are only modestly (T4) or not at all (TSH) lower than those found in controls

(Augustine 1967; Bleecker et al. 1969; Chopra et al. 1974; Green et al. 1977; Israel, Walfish, Orrego, Blake, and Kalant 1979; Israel et al. 1973; Murdock 1967; Nomura et al. 1975; Orrego et al. 1979; Ramakrishanan et al. 1976; Stokes 1971). The most likely mechanism involved appears to be a direct effect of alcohol on the peripheral conversion of T<sub>4</sub> to T<sub>3</sub> (Israel, Walfish, Orrego, Blake, and Kalant 1979), which takes place primarily in the liver (Oppenheimer et al. 1968, 1970).

Additional studies of the effects of acute or chronic alcohol administration on thyroid hormones have revealed an increased uptake of T<sub>3</sub> or T<sub>4</sub> into a number of target organs, particularly the liver, under both *in vivo* and *in vitro* conditions (Augustine 1967; Bleecker et al. 1969; Israel, Walfish, Orrego, Blake, and Kalant 1979; Israel et al. 1973; Patel et al. 1978; Ramakrishanan et al. 1976). Moreover, alcohol has also been reported to increase iodine uptake by the thyroid (Murdock 1967). Unfortunately, consistent results have not been obtained with either acute or chronic alcohol administration (Israel et al. 1973; Ramakrishanan et al. 1976; Sze et al. 1974; Wright 1978).

Alcohol does not appear to exert any important effects on the hypothalamic-pituitary aspects of the hypothalamic-pituitary-thyroid axis. When serum levels of the pituitary hormone TSH have been measured, they have generally been found to be unaltered after acute or chronic alcohol administration (Green et al. 1977; Israel, Walfish, Orrego, Blake, and Kalant 1979; Leppaluoto et al. 1975; Loosen and Prange 1977; Toro et al. 1973; Wright 1978; Wright et al. 1975, 1976). However, Wright et al. (1976) found a diminished TSH response to TSH-RH in about 10 percent of their chronic alcoholics, whereas most other indices of thyroid function were completely normal. The significance of this apparent refractoriness to TSH-RH stimulation in a small percentage of alcoholics is unclear, but on the basis of this study and those reviewed above, it appears that the effects of alcohol on the pituitary are slight indeed, if any occur at all. The levels of TRH have not been systematically measured in any study known to this reviewer, so it is impossible to assess whether alcohol exerts any effects on the neuroendocrine (hypothalamic) control of the pituitary-thyroid axis.

Although the foregoing studies suggest that alcoholics have relatively normal thyroid function, Goldberg (1960, 1962) reported that chronic alcoholics had a high degree of hypothyroidism, based on the low protein-bound iodine (PBI) levels found in their sera compared to a normal population, and an impaired response to TSH stimulation. Goldberg suggested that hypothyroidism was a significant feature of the clinical status of the alcoholic, and claimed a good clinical response in treating alcoholics with thyroid hormones (Goldberg 1960, 1962). On the basis of the large amount of data gathered since this initial report, however, it does not appear that alcoholics have hypothyroidism (see above and Augustine 1967; Selzer and Van Houten 1964; Wright et al. 1976) or that thyroid hormones have any utility in the treatment of alcoholism (Kalant et al. 1962; Satterfield and Guze 1961).



### *Consequences of Altered Thyroid Function*

Relatively few studies have examined the consequences of alcohol-induced alterations in thyroid function. Apart from the early clinical data referred to above, in which attempts were made to link abnormal thyroid function to alcoholism, there are only a few studies in which any attempt has been made to assess the consequences of alcohol-induced changes in thyroid activity. However, recent studies, particularly those by Breese, Prange, Nemeroff, and their associates, indicate that the administration of TRH to drug-naïve male rats significantly antagonizes the acute effects of alcohol (Breese et al. 1974; Cott et al. 1976; Mailman et al. 1978; Nemeroff et al. 1979; Porter et al. 1977; Yanagisawa et al. 1979). The effects of TRH on the development of tolerance to alcohol have not been examined, however. Apart from the innovative studies of these investigators, there are no other indications in the literature which would indicate that alcohol-induced alterations in the function of the thyroid participate in the drug's acute effects or in the development of tolerance and withdrawal behavior.

Israel and his colleagues have suggested an extremely important interaction between the thyroid and alcohol-induced liver disease (Bernstein et al. 1975; Israel, Kalant, Orrego, Khanna, Videla, and Phillips 1975; Israel, Khanna, Orrego, Rachamin, Wahid, Britton, MacDonald, and Kalant 1979; Israel, Videla, and Bernstein 1975; Israel et al. 1973). These investigators showed several years ago that chronic alcohol consumption produced a hypermetabolic condition in the liver that was accompanied by an increased rate of oxygen consumption (Bernstein et al. 1975; Israel, Videla, and Bernstein 1975; Israel et al. 1973). Since thyroid hormones have also been shown to produce a hypermetabolic state (Israel, Videla, and Bernstein 1975; Israel, Walfish, Orrego, Blake, and Kalant 1979; Israel et al. 1973), the investigators suggested that alterations in thyroid hormones may play a role in alcoholic hepatitis and cirrhosis (Israel, Videla, and Bernstein 1975; Israel, Walfish, Orrego, Blake, and Kalant 1979; Israel et al. 1973; Orrego et al. 1979). In support of this hypothesis they found that thyroidectomy virtually eliminated the hypermetabolic state induced by chronic alcohol administration in male rats (Bernstein et al. 1975; Israel, Videla, and Bernstein 1975) and that the antithyroid drug propylthiouracil (PTU) reversed the effects of alcohol on the liver (Bernstein et al. 1975; Israel, Kalant, Orrego, Khanna, Videla, and Phillips 1975).

On the basis of these studies in animals Orrego et al. (1979) and Israel et al. (in the two 1979 studies) have recently conducted double-blind clinical tests of the efficacy of PTU as a treatment modality in patients with alcoholic liver disease. In agreement with much of the work described above, they found that T3 levels were markedly lower in their alcoholic subjects (Israel, Walfish, Orrego, Blake, and Kalant 1979) than in controls and found an excellent inverse correlation between serum T3 levels and the extent of liver damage (Israel, Walfish, Orrego, Blake, and Kalant 1979; Orrego et al. 1979). The administration of PTU



was found to provide an excellent degree of reversal of liver damage in chronic alcoholics and was most effective in patients with the lowest serum T3 levels and most severe liver damage (Israel, Walfish; Orrego, Blake, and Kalant 1979; Orrego et al. 1979). Patients with normal T3 levels did not respond effectively to PTU treatment.

These studies are extremely important from a clinical viewpoint for two reasons. First, serum T3 may provide a good screening device to assess alcoholic liver damage, although it should be noted that other conditions also give rise to elevated serum T3 (Bermudez et al. 1975; Israel, Walfish, Orrego, Blake, and Kalant 1979; Schimmel and Utiger 1977) which may limit its usefulness to a certain degree. Second, PTU may provide the first established clinically efficacious treatment for one of the most devastating consequences of alcoholism (i.e., alcoholic hepatitis and cirrhosis). However, more work is obviously required to establish the effectiveness of PTU (e.g., side-effects, dosage schedules, etc.) and to more clearly elucidate its mode of action. Nevertheless, these are extremely important findings and may represent a major clinical breakthrough in the management of the biomedical complications associated with alcoholism. In addition, the results of Israel and colleagues (Israel, Walfish, Orrego, Blake, and Kalant 1979; Orrego et al. 1979) suggest that the now dormant interest in alcohol-thyroid interactions should be given new life.

## ***Growth Hormone***

### *Direct Effects of Alcohol on Growth Hormone Release*

The evidence regarding the effects of acute and chronic alcohol administration on basal growth hormone levels in humans appears to be equivocal at the present time. Various investigators have found increases, decreases, or no change in steady-state growth hormone levels in human males following acute alcohol administration (Andreani et al. 1976; Arky and Freinkel 1964; Bagdade et al. 1972; Bellet, Yoshimine, Decastro, Roman, Parmar, and Sandberg, 1970; Leppaluoto et al. 1975; Toro et al. 1973). However, there appears to be good agreement that alcohol acutely blocks stimulated growth hormone release (e.g., by environmental stimuli, hypoglycemia, or L-dopa chemotherapy) in normal males and chronic alcoholics (Andreani et al. 1976; Arky and Freinkel 1964; Bagdade et al. 1972; Bellet, Yoshimine, Decastro, Roman, Parmar, and Sandberg 1970; Blackard et al. 1971; Chalmers et al. in press; Ganda et al. 1978; Priem et al. 1976; Quabbe et al. 1972; Riesco et al. 1974). These data suggest that chronic alcohol administration may alter the responsiveness of the growth hormone system to environmental and physiological stimuli that provoke its release. There are essentially no systematic studies of the effects of alcohol on growth hormone release in animals. From the single study available (Ratcliffe 1972), however, it does not appear that alcohol

exerts any important effects on basal, nonstimulated growth hormone levels. It is not known whether alcohol decreases stimulated growth hormone release in animals as it does in humans. Finally, there have been no attempts to localize the action of alcohol on growth hormone release to the hypothalamus or pituitary up to the present time.

### *Consequences of Alcohol-Induced Alterations in Growth Hormone*

No studies in the literature indicate that changes in growth hormone secretion after acute or chronic alcohol administration result in functionally important effects in terms of the acute and chronic actions of alcohol. It seems obvious, however, that persistent depressions in the secretion of this critical anterior pituitary hormone would have significant effects on many physiological and biochemical processes.

## ***Prolactin***

### *Direct Effects of Alcohol on Prolactin Release*

There are very few studies of the effects of alcohol on prolactin release in the human male. Several groups of investigators have found increases in prolactin levels in normal volunteers after acute alcohol administration and in the drinking chronic alcoholic (Earll et al. 1976; Gordon and Southren 1977; Mendelson et al. 1980; Van Thiel and Lester 1974; Van Thiel, Gavalier, Lester, Loriaus, and Braunstein 1975; Van Thiel et al. 1978; Williams 1976; Wright 1978; Yen et al. 1974; Ylikahri et al. 1976, 1978), but not all investigators have observed such changes (Cushman and Kreek 1974; Gordon and Southren 1977; Toro et al. 1973; Loosen and Prange 1977; Turkington 1972). Furthermore, resting levels of prolactin in abstinent chronic alcoholics have been found to be normal or slightly reduced in the few studies available (Loosen and Prange 1977; Wright 1978).

Ylikahri et al. (1976, 1978) found that the prolactin release in response to TRH was significantly enhanced during periods of peak blood alcohol levels in normal volunteers. On the other hand, two groups of investigators have found that the prolactin response to TRH administration (increase) was blunted during withdrawal from alcohol in chronic alcoholics (Loosen and Prange 1977) or 10 hours after the administration of a very high dose of alcohol ("the hangover period") in normal human volunteers (Ylikahri et al. 1976, 1978).

Taken as a whole, these acute and chronic studies in humans seem to indicate that (a) acute alcohol administration tends to increase prolactin in normal volunteers; (b) basal, resting levels in the alcoholic are normal or modestly lower than those found in controls; and (c) prolactin response to TRH may be enhanced by acute alcohol administration but may be blunted during the "hangover" period or in

the chronic alcoholic undergoing withdrawal. It should be obvious, however, that these conclusions are general and tentative, and not all of the data are consistent with these interpretations (see above).

Chronic alcohol administration appears to elevate serum prolactin levels in rats (Cicero 1980c; Gordon and Southren 1977), but this issue has not been examined in any depth. No studies are available in which acute alcohol administration has been examined.

Regarding alcohol's site of action within the hypothalamic-pituitary axis, it has been reported that alcohol increases prolactin release by the anterior pituitary under *in vitro* conditions (Thorner et al. 1978). These data seem to provide the only available evidence regarding the locus of action of alcohol, and they seem to implicate an exclusive pituitary site of action. This conclusion should be interpreted cautiously, however, since rather high levels of alcohol were required in this *in vitro* study, and it is a single report.

A major problem in interpreting any study of drug-induced alterations in prolactin is that it is difficult to differentiate drug-specific effects from the nonspecific effects of stress. Since prolactin levels rise dramatically in response to stress in many species (Carroll 1978; Frantz et al. 1972) and alcohol itself may be a stressor, particularly when given in intoxicating amounts, the significance of alcohol-induced changes in prolactin must be interpreted with caution.

### *Consequences of Alcohol-Induced Alterations in Prolactin*

So far there have been no studies that would suggest that alterations in serum prolactin levels have any significance in relation to the effects of alcohol. Since changes in prolactin levels after acute or chronic alcohol administration are not well documented, it may not be surprising that there has been little speculation about their significance. However, Van Thiel and associates (Van Thiel and Lester 1974; Van Thiel, Gavalier, Lester, Loriaus, and Braunstein 1975; Van Thiel et al. 1978) have suggested that increased prolactin levels in chronic alcoholics might participate in the "feminization," particularly gynecomastia, observed in these individuals. Also, Williams (1976) has suggested that alcohol-induced increases in prolactin may contribute to a higher degree of breast cancer in alcoholics. At present, however, there are no convincing data to establish this relationship unequivocally. There are no other reports on the consequences of alcohol-induced alterations in serum prolactin levels.



## ***Vasopressin***

### *Direct Effects of Alcohol on Vasopressin Release*

There seems to be little question that acute alcohol administration or ingestion produces diuresis in male and female animals and humans (Bisset and Walker 1957; Cobo and Quintero 1969; Eggleton 1942; Haggard et al. 1941; Kleeman 1972; Kozlowski et al. 1967; Marquis et al. 1975; Strauss et al. 1950). It seems equally clear that alcohol produces this effect by inhibiting the secretion of vasopressin. This conclusion is based on two sets of observations. First, alcohol-induced diuresis can be overcome by the administration of synthetic vasopressin (Eggleton 1942; Haggard et al. 1941; Kleeman 1972). Second, several groups have shown that serum vasopressin levels are markedly reduced in normal human volunteers and animals after acute alcohol administration on the ascending slope of the blood alcohol curve when diuresis is most prominent (Beard and Knott 1971; Bisset and Walker 1957; Helderman et al. 1978; Linkola et al. 1977, 1978; Marquis et al. 1975; Sereny et al. 1966). During chronic alcohol administration little or no tolerance seems to develop to the antidiuretic effects of alcohol or its inhibition of vasopressin release (Marquis et al. 1975; Sereny et al. 1966). The actions of alcohol on vasopressin release have also been studied during alcohol withdrawal in chronic alcoholics or on the descending limb of the blood alcohol curve after acute administration. Generally "rebound" increases in vasopressin have been found in these studies (Bisset and Walker 1957; Linkola et al. 1978; Marquis et al. 1975).

The locus of alcohol's actions on vasopressin release appears to be at a point at or above the posterior pituitary-supraoptic nucleus of the hypothalamus. The evidence in support of this conclusion can be summarized as follows. First, stimuli that normally cause vasopressin release, such as a sodium chloride load (Kleeman 1972; Kozlowski et al. 1967) or direct application of acetylcholine to neurons in the supraoptic nucleus in the hypothalamus (Bisset and Walker 1957), can override the diuretic effects of alcohol. Second, alcohol inhibits the histological changes in vasopressin-containing cells of the supraoptic nucleus produced by a large dose of sodium chloride in animals (Raiha 1960). Finally, alcohol inhibits the electrically evoked discharges of the supraoptic secretory cells in the hypothalamus (Miller and Mill 1967). This action is not due to a direct effect of alcohol on these cells, however, since they respond very well to direct stimulation (see the first and second points above). Alcohol's effects on vasopressin release therefore seem to be due to an action at some neuronal locus above the neurosecretory cells.



*Consequences of Alcohol-Induced Alterations in Vasopressin Levels*

Although there are few data linking acute changes in vasopressin to the acute pharmacological effects of alcohol (aside from diuresis), there is a growing body of evidence suggesting that vasopressin and other centrally active peptides may play a significant role in the development of tolerance and physical dependence. Hoffman and coworkers (1978, 1979) reasoned that vasopressin might play some role in the acquisition and maintenance of tolerance to alcohol because of three observations. First, several groups have shown that many peptides in brain, including vasopressin, have significant biological activity, particularly with respect to the acquisition and retention of certain learned behaviors in rats (DeWied 1971; DeWied and Gispen 1976; DeWied et al. 1972; Rigter and Crabbe 1979). Second, vasopressin and its analogs have been shown to alter the acute effects of psychoactive drugs and the development of tolerance (Niesink 1981; Van Ree and DeWied 1976, 1977), although it should be noted that there is some controversy in this area (Mello and Mendelson 1979). Third, there is a good deal of evidence suggesting that the development of tolerance to alcohol may be influenced by learning or performance variables (Chen 1972; LeBlanc et al. 1973, 1976; Wenger et al. 1980).

In view of these observations and the fact that alcohol alters serum vasopressin levels, Hoffman et al. (1978, 1979) speculated that the administration of arginine vasopressin (AVP) or its synthetic analog des-9-glycinamide lysine vasopressin (DGLVP) might alter either the acquisition or maintenance of tolerance to alcohol. These investigators maintained rats on an alcohol-containing liquid diet for 12 days. Half of the animals received AVP subcutaneously each day and then for several days following withdrawal from the alcohol diet. The results of these studies indicated that tolerance to the hypothermic effects of alcohol persisted longer after discontinuation of alcohol treatment in AVP-treated rats than it did in control-injected animals. Moreover, these investigators found that only the retention and not the acquisition of tolerance was affected by AVP administration (i.e., AVP-treated animals attained the same level of tolerance at apparently the same rate). Of some importance in these studies, AVP did not influence the maximum blood alcohol concentrations reached during the tolerance induction phase or alter the rate of alcohol metabolism.

The observations of Hoffman et al. (1978, 1979) have subsequently been replicated and extended by Rigter and Crabbe (1979, 1980; Crabbe and Rigter 1980). In their studies they found that the intracerebroventricular administration of DGAVP (an AVP analog with little peripheral activity), throughout a period of alcohol exposure, significantly increased the persistence of tolerance, as measured by hypothermia, relative to controls. In their hands, however, tolerance persisted for only 1 day, rather than the 2 days reported by Hoffman et al. (1978, 1979). They concluded that the difference between the two groups was based

on the fact that tolerance dissipates very rapidly with the inhalation model when compared to the liquid-diet technique employed by Hoffman and associates. In all other respects, however, both groups appear to have produced equivalent results.

Several other factors should be pointed out regarding the effects of vasopressin on the maintenance of tolerance. First, vasopressin had to be administered during the exposure to alcohol—there was no effect of the compound on tolerance if it was given only during the testing phase. Second, vasopressin itself had no effect on the measure (hypothermia) used to assess tolerance in either study. Third, as alluded to above, vasopressin did not alter the peak blood levels of alcohol or its rate of metabolism during the induction phase in either study (Crabbe and Rigter 1980; Hoffman et al. 1978, 1979; Rigter and Crabbe 1979, 1980).

The effects of vasopressin on alcohol withdrawal symptoms have also been examined. On this point, however, there is some controversy. Hoffman et al. (1978, 1979) reported that vasopressin did not affect withdrawal signs and reactions in their animals. On the other hand, Rigter and Crabbe (1979, 1980; Crabbe and Rigter 1980) found that the intraventricular injection of DGAVP markedly increased both tolerance persistence and withdrawal symptomatology. There is no apparent explanation for this difference.

## **Oxytocin**

### *Direct Effects of Alcohol on Oxytocin Levels*

Oxytocin levels have not been directly measured after acute or chronic alcohol administration up to the present time in man or animals because a sensitive technique is lacking. However, on the basis of results inferred from bioassays, such as the milk-ejection response in lactating females or uterine contractions associated with nursing, alcohol appears to inhibit the release of oxytocin in a dose-dependent fashion (Fuchs 1966, 1969; Fuchs and Wagner 1963; Wagner and Fuchs 1968). Whether alcohol inhibits oxytocin levels in the male has not been examined, which in part may be due to the fact that its role in the male is not at all well understood. Consequences of Alcohol-Induced Changes in Oxytocin

Essentially nothing is known about the consequences of alcohol-induced reductions in oxytocin levels in blood or its target organs. There appears to be only one study in which this issue has been examined. Hoffman et al. (1979) examined whether the administration of oxytocin during chronic alcohol administration altered either the acquisition, expression, or persistence of alcohol tolerance and withdrawal and found no effects of oxytocin on any of these parameters. Clearly, more studies are needed in this area, particularly since oxytocin has now been found to be widely distributed in discrete pathways in brain, projecting from the hypothalamus (Swanson 1977). This suggests an

important role for this compound, other than those normally ascribed to it, in brain function. Studies of alcohol's effects on this system and the consequences of any observed alterations in its activity therefore may be quite informative.

### ***Involvement of Endogenous Opioid Peptides in Neuroendocrine Function***

Narcotic drugs significantly influence a variety of neuroendocrine systems (Cicero 1979, 1980*b,c*) and appear to increase the secretion of many hormones and markedly depress the release of others. Moreover, it has been shown by many investigators that the narcotics interact with specific opiate receptors in the hypothalamus to exert their neuroendocrinological effects (Cicero 1979, 1980*b,c*). The existence of opiate receptors in the brain suggests that they are not present simply to interact with narcotic drugs but that there may be endogenously occurring substances that normally have an affinity for them. In support of this conclusion, over the past 5 years a host of opiate-like compounds (termed "endogenous opioid peptides") have been discovered in brain (Cicero 1979, 1980 *b,c*; Guillemin 1978). Since narcotic drugs exert several important neuroendocrine effects, the discovery of endogenous opioid peptides has quite naturally led to the suggestion that they, too, might be involved in the regulation of neuroendocrine events. The results of many studies suggest that this is indeed the case. Thus far, endogenous opioid compounds have been implicated in the neuroendocrine control of luteinizing hormone, prolactin, growth hormone, ACTH, and several other endocrines (Cicero 1979, 1980*b,c*; Guillemin 1978; Mirin et al. 1976). Furthermore, they appear to participate in the normal regulation of activity in these neuroendocrine axes and also in the complex feedback controls of these systems. Consequently, it appears that endogenous opioid peptides are intimately involved in a host of neuroendocrine systems.

The possibility that alcohol may perturb endocrine function by disrupting neurons containing endogenous opioid peptides has not yet been examined in any detail, but since these substances are important regulators of neuroendocrine activity, such studies should be assigned a high priority. Moreover, since alcohol or its immediate metabolite, acetaldehyde, may condense with certain compounds in brain to form alkaloid substances of the narcotic class (Cicero 1980*a*), it may be that these compounds (if generated in significant quantities in brain) could exert direct narcotic-like effects themselves on various neuroendocrine systems. This possibility seems plausible since it appears that, in general, the neuroendocrine effects of alcohol and the narcotics are remarkably similar. These observations are clearly speculative at this point, however, and the entire area of alcohol-endogenous opioid interactions needs to be carefully examined.



## ***Conclusions and Suggestions for Future Research***

This state-of-the-art review has described the available studies concerning the impact of alcohol on a variety of neuroendocrine systems, the possible involvement of induced alterations in endocrine state in the acute effects of alcohol, the biomedical complications associated with long-term use, and the development of tolerance and withdrawal behavior. It should be apparent that we know relatively little about the effects of alcohol on the full range of neuroendocrine systems.

A good deal is known about the effects of alcohol on the hypothalamic-pituitary-gonadal axis and much less so on all of the remaining neuroendocrine axes. Clearly, we need to know much more about the effects of alcohol on the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes and upon growth hormone, vasopressin, and oxytocin release, as well as several other neuroendocrines that have been virtually ignored. Furthermore, a number of questions remain concerning the effects of alcohol on all of the neuroendocrine systems discussed in this review, including the role of endogenous opioid peptides in neuroendocrine function and the endocrine effects of alcohol.

It is hoped that research in these important areas will be greatly accelerated in the coming years. Since the endocrinological techniques are presently available to explore the effects of alcohol on any neuroendocrine system, and animal models are available to examine the acute and chronic actions of alcohol, it appears that this is an eminently researchable area. At present the only thing that appears to be lacking is a "critical mass" of investigators interested in examining alcohol-endocrine interactions.

The significance of alcohol-induced changes in endocrine state is only now being appreciated. This is somewhat surprising in view of the fact that hormones play such an integral role in the cellular biochemistry and physiology of every organ in the body. It is virtually unimaginable that significant alcohol-induced alterations in the secretion of any hormone, therefore, would not have profound significance both with respect to the acute pharmacological actions of the drug and the long-term consequences associated with its use (i.e., biomedical complications and the development of tolerance and physical dependence).

Indeed, when investigators have explored the ramifications of altered neuroendocrine function resulting from acute and chronic alcohol administration, they have found very significant alcohol-endocrine interactions. For example, the innovative studies regarding the significance of alcohol-induced alterations in the hormones of the hypothalamic-pituitary-gonadal axis with respect to alcoholic liver disease and the development of metabolic tolerance are extremely important both clinically and basically. Likewise, the recent studies regarding the role of alterations in the secretions of the hypothalamic-pituitary-adrenal axis



and in vasopressin release in the development of alcohol tolerance and withdrawal behavior have indicated a potentially important interaction. Thus, in virtually every study conducted up to the present time, significant interactions have been found between alcohol-induced changes in endocrine state and the acute and chronic effects of the drug. This strongly validates the assumption that changes in endocrine state are integrally involved in alcohol's acute and chronic effects in many organ systems. In the next few years, further extremely exciting and important breakthroughs can be expected—provided, of course, that investigators seize the opportunity to examine these important issues.

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## **Chapter 4**



# **Neurophysiological Changes Produced by Alcohol**

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## **Abstract**

Ethanol, as a depressant capable of interacting with nerve cell membranes, can profoundly alter central nervous system (CNS) function. When administered acutely, ethanol acts in a biphasic, dose-dependent manner such that very low doses of ethanol increase neural excitability in many brain regions, while higher doses produce the more well-known sedative effects. Many laboratory studies, attempting to define the primary sites of ethanol's acute effects within the brain, have supported a regional hierarchy of susceptibility ranging from primary sensory neurons as least affected to association cortex and reticular formation as most affected. However, a general disruptive effect at synapses throughout the brain has not been ruled out. When ethanol is repeatedly administered, both tolerance and physical dependence develop. Tolerance is seen to both the sedation and the sleep disturbances produced by ethanol. During the period of continuous exposure, the CNS also develops a latent state of neural hyperexcitability. This state is one component of physical dependence and becomes evident both behaviorally and neurophysiologically during withdrawal. Neurophysiologically, the withdrawal reaction consists of epileptiform activity diffusely organized in cortical and subcortical loci. Although hyperexcitability is not observed in all brain regions, neither is its genesis confined to one area within the brain.

Although most aspects of intoxication and withdrawal subside shortly following ethanol removal, chronic ethanol exposure can produce persistent residual CNS dysfunction. Features of this brain damage include alterations in spontaneous and evoked neural activity, performance declines on psychometric tests, and neuropathology. At present, it is unclear how ethanol-induced damage to specific brain structures correlates with specific cognitive impairments. Neurophysiological studies of the altered neural activity from these brain regions will serve as an essential link between the neuropathology and the neuropsychological abnormalities.



## Introduction

This report focuses on the neurophysiological changes occurring in the central nervous system (CNS) of man and animals after acute and chronic alcohol exposure. A basic understanding of how alcohol influences the CNS of man must begin with fundamental knowledge of its basic mechanism of action on nerve cells. In this first section we briefly review some important properties of nerve cells and their interaction with ethanol. Such information has been almost exclusively derived from invertebrate and simple vertebrate neuronal systems.

### *Basic Properties of Neurons*

Nerve cells can be considered as chemically differentiated components within a bioelectric system. The membrane of a nerve cell exhibits a resting voltage or potential (inside negative) due to two factors: (1) a significantly greater resting membrane permeability to potassium ions ( $K^+$ ) as compared to sodium ions ( $Na^+$ ) and (2) an ion-exchange pump that maintains the differences in concentration existing across the cell membrane for each ionic species. In nerve cells, whenever permeability to  $Na^+$ ,  $K^+$ , or other ions changes, electric current flow is generated as these ionic species flow from regions of high concentration to regions of low concentration.

A nerve cell can be divided simplistically into three functional regions: an input zone, a conductive zone, and an output zone. The *input zone* (dendrites, cell body) on a nerve cell has specialized membrane regions containing receptor sites that respond to specific neurotransmitters. Activation of these receptors opens membrane channels for certain ions. Current flow occurs at these sites and can be either depolarizing (excitatory) or hyperpolarizing (inhibitory) relative to the resting potential. Nerve cells contain thousands of receptor sites (synapses) and the various synaptic currents summate spatially and temporally along the membrane of the input region.

The *conductive zone*, or axon, has a membrane with specialized channels for  $Na^+$  and  $K^+$  that are uniquely sensitive to fluctuations in the resting potential. A specialized region of the axon serves as the site for initiation of the action potential. When the membrane in this region becomes sufficiently depolarized as a result of excitatory current flow in the input region, voltage sensitive channels for  $Na^+$  and  $K^+$  are opened. The action potential consists of a distinct *sodium current* which rapidly depolarizes the membrane and a slower potassium current which aids in repolarizing the membrane back to resting membrane levels. Once initiated, the action potential is conducted in an "all-or-none" fashion along the length of the axon in a manner that can be likened to a burning fuse.

The *output zone* of a nerve cell occurs at the terminal regions of the axon. Nerve cells communicate at specialized regions called synapses. The axon terminals of the synapse contain specialized vesicles in which

chemical agents termed neurotransmitters are stored. When the action potential invades the axon terminal a process is triggered that involves mobilization of the vesicles and release of the transmitter into a narrow synaptic cleft. This process requires calcium. The transmitter then diffuses across the cleft to influence receptor sites on the next cell. It should be emphasized that this is a simplified version of the functions of a nerve cell. Many other variations have been reported which further complicate this picture, particularly regarding synaptic transmission. However, ethanol appears capable of altering each of these processes in the CNS of man.

### *Cellular Actions of Ethanol*

Ethanol is almost universally acknowledged to exert its effects on the CNS through interaction with neuronal membranes. Ethanol is but one of a variety of chemically dissimilar agents that can produce CNS depression and anesthesia. The property these agents share is that concentrations required to produce anesthesia are highly correlated with their solubility in lipids. The classical Meyer-Overton rule states that anesthesia occurs whenever a certain molar concentration is attained in the lipid phase of the neuronal membrane, but it now appears that the molar concentration provides only an initial approximation of the potency of various anesthetics. A considerable body of literature has sought to correlate anesthetic potency with a variety of other biophysical properties of the alcohols and other depressants (Seeman 1972). This correlative approach can only establish the molecular requirements of an anesthetic molecule but has already established that the depressants must act upon hydrophobic membrane sites (i.e., sites lacking an affinity for water). Thus, ethanol could act on hydrophobic portions of membrane lipids, proteins, or lipid-protein interfaces.

Chin and Goldstein (1977b), using spin label resonance techniques, reported that ethanol increases the fluidity or disorder of a variety of membrane preparations obtained from mice. They showed further that membrane preparations from ethanol-tolerant mice were resistant to this fluidizing action (Chin and Goldstein 1977a). These results were later supported by the observation that ethanol increases the fluidity of artificial membranes containing only lipid molecules (Vanderkooi 1979). Chronic ethanol treatment in the mouse decreases the concentration of unsaturated fatty acids in phospholipids from synaptic membranes, consistent with an adaptive membrane response to the acute fluidizing action of ethanol (Littleton et al. 1979). These results have been interpreted to indicate that the primary action of ethanol is on the fluidity of membrane lipids. The data require careful scrutiny, however, particularly in view of the presence of conflicting data (Ingram 1976).

The fluidity or mobility of lipid molecules appears to be an extremely important aspect of membrane function and is influenced by a variety of factors including: (1) the type of phospholipids present and their fatty acid composition, (2) the presence of protein, which exerts a strong

immobilizing force on lipids, and (3) the binding of calcium to the membrane (Chapman 1975; Lenaz et al. 1975). Additionally, others have emphasized ethanol-induced alterations in membrane protein (Noble et al. 1976; Ross et al. 1977) or in calcium binding (Ross 1977) which could alter membrane fluidity indirectly. Collectively, these studies have introduced an important field of inquiry and promise to provide even greater insight into ethanol interactions with membrane function.

Since ethanol probably invades all portions of neuronal membranes, it is not surprising that ethanol is capable of altering a variety of physiological processes. The results of many studies indicate that ethanol can disrupt four major neuronal processes: (1) it induces a specific reduction in neural excitability by reducing the sodium current underlying the action potential (Armstrong and Binstock 1964; Faber and Klee 1977); (2) it produces varied effects on the resting membrane potential of nerve cells by altering the resting permeability (Knuttsen and Katz 1967) and the active transport (Kalan and Israel 1967) of  $\text{Na}^+$  and  $\text{K}^+$ ; (3) it stimulates neurotransmitter release (Curran and Seeman 1977); and (4) it exerts dose-dependent increases (Gage et al. 1975) or decreases (Adams et al. 1977) on the excitatory currents underlying postsynaptic potentials in different neuronal systems.

The concentrations of ethanol required to produce these effects greatly exceed those known to be lethal in vertebrate CNS, leading some to question the relevance of these data to the human condition. The important point to focus on when considering the above data is that they illuminate the basic neuronal processes most likely to be susceptible to ethanol-associated disruption in the vertebrate CNS. Further, it is apparent that a concentration-dependent gradient of susceptibility exists for disruption by ethanol. For example, ethanol alters synaptic transmission at concentrations substantially below those that reduce the magnitude of the action potential (Faber and Klee 1977), while the resting membrane potential is altered at still higher concentrations (Armstrong and Binstock 1964). Finally, even at identical concentrations ethanol variably influences different cell types depending upon their intrinsic membrane characteristics (Faber and Klee 1977). It is clear that no single model neuronal system can provide definitive evidence of the primary neuronal processes disrupted by ethanol. This can be achieved only through study of nerve cells in more complex vertebrate brains. Yet model systems have provided significant information on which to focus neurophysiological and biochemical studies of these more complex neuronal systems.

### *The Scope of Neurophysiology and Its Relation to Alcohol Research*

Neurophysiology has evolved during the past half century to the point where it is both diverse in its scope and highly quantitative and sophisticated in its analysis capability. Only during the past two decades have neurophysiological measures been applied to the study of the



effects of ethanol on the nervous system. Before discussing some of the major findings emerging from this research area it is necessary to consider briefly the scope of neurophysiological analyses that have been or could be used in the study of ethanol-associated nervous system changes.

The most widely used and best known neurophysiological tool is the electroencephalogram (EEG). EEG measures either are made directly from brain tissue via surgically implanted recording electrodes or, alternatively, are recorded from the scalp surface. In the former case, continuous monitoring of the patterns of voltage changes occurring between populations of surrounding neurons can be made throughout the brain mass, including its deepest and most sequestered recesses. In the latter case (scalp electrodes) the predominant source of electrical activity is the brain surface, or cortex, rather than the deep subcortical regions.

Electroencephalographers have described extensively the EEG during both wakefulness and sleep. These patterns or "rhythms" have been classified in terms of their dominant frequency described: delta (1-3 Hz); theta (4-7 Hz); alpha (8-12 Hz); beta (13-30 Hz); and gamma (above 30 Hz). These rhythms vary in their relative dominance and in the regions of cortex where they predominate. Computer analysis of EEG rhythms has provided important new dimensions for their scientific and clinical usefulness. Thus automated computer analysis of the energy or power contained within specific frequency bands is now common. Other computer-based analyses such as auto- and cross-correlational techniques provide additional insights into the coherence and phase relationship of particular EEG events.

During normal sleep the EEG passes through a number of patterns that have been designated as the hallmark of a number of "stages" of sleep, ranging from light drowsiness to deep sleep. For the purpose of this review only two categories of the sleeping EEG are considered: the synchronous low-frequency EEG stages known collectively as slow wave sleep (SWS) and the desynchronized low-voltage high-frequency EEG pattern known either as rapid eye movement (REM) or paradoxical sleep. As we discuss below, the study of EEG changes during sleep in alcoholic subjects has provided interesting and important findings.

Another major neurophysiological tool is the evoked potential (EP) technique in which small potentials (voltage changes) are typically evoked by an applied stimulus under experimental control. For example, a flash of light, a brief tone, a tap to the skin, or an electrical stimulus delivered directly to some region of nervous system could each serve as the stimulus capable of evoking a time-dependent potential recorded between two electrodes monitoring neural activity.

The EP represents the summated slow excitatory and inhibitory post-synaptic potentials (EPSPs and IPSPs, respectively) and fast (spike or action potentials) activity occurring in a limited region of neural tissue during a relatively brief (500 ms or less) period of time.



The advantages of this tool are numerous: The investigator has control over the parameters of the stimulus and the time of stimulus application, and this control enables the investigator to establish a temporal reference point useful in the subsequent analysis of data. Thus, in contrast to the EEG which is a continuously ongoing and ever-fluctuating stream of voltage changes, the EP will occur only following the application of a suitable stimulus. Repeated application of that stimulus leads to repeated elicitation of the EP. Computer-aided averaging and analysis of the EP are greatly facilitated by these constraints.

Both EEG and EP recordings are easily obtained from experimental animals or human subjects. Neither of these neurophysiological tools requires surgical intervention. In order to obtain more precise information regarding the specific nature of the underlying neuronal changes direct microelectrode recordings of nerve cell activity are necessary. These recordings require surgical preparation and therefore are used in humans only during situations requiring neurosurgical procedures for clinical reasons. Animal experiments, however, have made extensive use of direct monitoring of nerve cell activity.

The macropotential recordings provided by either EEG or EP allow analysis of a "voltage envelope" of complex underlying neural activity. No specific information can be obtained from these methods regarding the actual types of changes occurring among the many hundreds or thousands of neurons contributing to the overall voltage envelope. The advantage of directly monitoring the activity of either small clusters of neurons (multiple unit activity [MUA]) or single neurons is that the electrode provides a window from which to sample specific changes in cellular activity patterns.

A more recent neurophysiological method called iontophoresis represents yet another way in which individual neurons can be monitored. Iontophoresis utilizes micropipettes having extremely small tip diameters. These pipettes can be filled with chemical substances of infinite variety. By ejecting microquantities of a given substance either onto or into neurons, the activity change of the neuron can be measured. Such a method can provide information about the level of neurotransmitter receptor sensitivity in a neuron as well as other fundamental ionic mechanisms of membrane regulation.

The disadvantages of such microelectrode recording techniques are the invasive procedures they require and their ability to sample the activity of only a few selected neurons. Such limited sampling may exclude a great number of cells and perhaps cell types that may show different changes than those actually sampled.

### *Clinical Applicability and Research Importance of Neurophysiological Measures*

Application of various neurophysiological measures in human alcoholic patients or experimental subjects is both real and important.

Considerable diagnostic and prognostic information can be obtained through such measures. For example, as described in more detail below, certain EEG abnormalities recorded during sleep may be a reliable correlate of alcohol dependence and/or tolerance. Acquiring these important data does not require invasive procedures, lengthy hospitalization, or any risk to the subject.

The determination of baseline EEG parameters coupled with longitudinal EEG studies extending from the period of alcoholization through withdrawal and into an extended dry-out period may provide an accurate measure of the extent of recovery and return of normal brain electrical activity.

Another advantage of the EEG derives from its unique status as a moment-to-moment indicator of consciousness. Altered mental and physical states are generally reflected in particular types of EEG changes. Through the use of biofeedback the EEG might be used as an effective cue enabling alcoholics or potential alcoholics to alter their state of consciousness in such a way as to obviate the need to do so with ethanol. While presently such a suggestion is clearly speculative, it does suggest one direction the application of such neurophysiological techniques might take.

What are the disadvantages and limitations of neurophysiological techniques in alcohol treatment and research? One limitation is that only certain brain regions are likely to be monitored. Particularly in human applications, where noninvasive techniques are all but mandatory, only limited surface regions of brain are easily accessible for screening and the extensive subcortical mass is likely to go unexplored. This limitation is one of the reasons animal experimentation is essential for a more complete understanding of the effects of ethanol on the CNS.

Another limitation is that uncontrolled variables can contribute to abnormalities in the data. For example, other processes associated with alcoholism, such as malnutrition or aging, might result in EEG or other neurophysiological abnormalities erroneously linked to an ethanol etiology. While this limitation also exists in biochemical, physiological, behavioral, and other types of measures, it may not be as readily discerned in neurophysiological data. For these and other reasons it is important to realize that a well-controlled experimental animal model for the study of the biological and behavioral effects of ethanol is an essential link in the basic science-clinical science continuum required to achieve a complete understanding of the effects of alcohol on the nervous system.

### *Dimensions of Alcohol Actions on the Brain*

As a drug commonly abused for prolonged periods, ethanol presents several dimensions of action on the brain. This report separately considers three dimensions of ethanol and brain function.

1. Acute actions—Ethanol is a general depressant and produces changes in the EEG of man and animals consistent with this category of drugs. Evidence for a stimulant effect of ethanol at low doses has also been reported, and emphasizes the need for careful consideration of the pharmacokinetic properties of ethanol in these studies including dose, route, and speed of administration.
2. Tolerance and physical dependence—Tolerance is defined as a reduction in the acute effects of ethanol after repeated exposure. Physical dependence is present when a physiological disturbance occurs after withdrawal following a period of chronic alcohol abuse. Tolerance and physical dependence have been reported to follow chronic exposure in man and animals (Isbell et al. 1955; Kalant et al. 1971; Wikler et al. 1956). Tolerance and physical dependence have traditionally been considered to reflect the same or similar neural adaptive process. This adaptive process serves to counteract the acute actions of ethanol (resulting in the development of tolerance). Upon abstinence the adaptive process itself constitutes a neural imbalance and underlies the appearance of the withdrawal reaction. While this view has enjoyed great appeal, the development of tolerance and physical dependence have now been dissociated experimentally (Tabakoff and Ritzmann 1977). However, the significance of these observations must await future research.
3. Chronic toxicity of ethanol—Chronic alcohol abuse is associated with brain damage. While the development of physical dependence occurs over a period measurable in days (Wikler et al. 1956), the neurotoxic actions of ethanol become apparent only after years of heavy abuse. The hallmark of the toxic actions of ethanol is that the effects are permanent and are unrelated to the intervening period of alcohol abstinence. Neurophysiological studies of chronic toxicity in man are complicated by coexisting development of physical dependence which produces overt behavioral signs for only a few days following withdrawal but may produce residual impairment which is detectable in neurophysiological measures for prolonged periods.

For each of these dimensions we will consider the phenomenology of neurophysiological changes observed after acute and chronic alcohol exposure and the localization of these changes, i.e., where in brain does alcohol produce its effects.

### ***Neurophysiological Studies of the Acute Actions of Ethanol***

The magnitude of the social problems created by alcoholic intoxication requires us to understand ethanol's acute actions on the central



nervous system. To achieve this end we must address three major issues: (1) What are the effects of acutely administered ethanol on CNS functioning? (2) Where in the CNS does ethanol primarily act? (3) How does ethanol affect neuronal functions in a molecular biological sense? The cellular actions of ethanol were discussed in a previous section of this report. There is today a considerable amount of research evidence enhancing our understanding of the remaining two questions.

### *Phenomenology of Ethanol's Acute Action in the CNS Human Studies*

Since the early work of Loomis et al. (1936), a large number of investigators have reported that in man, acute ethanol administration results in a slowing of the EEG (i.e., a shift to lower frequencies) (Engel et al. 1945; Holmberg and Martens 1955; Lehtinen et al. 1976; Rosadini et al. 1974). The most prominent effect is a progressive slowing of the dominant alpha frequency as well as an increase in amplitudes of the slower frequencies occurring at blood ethanol concentrations of 50.0-200.0 mg/100 ml. Thus these experiments generally report an increase in the alpha band frequencies and a corresponding decrease in the faster frequencies such as those in the beta range (13-30 Hz). More severe intoxication leading to drowsiness and sleep is accompanied by diffuse high voltage slow wave activity. These findings indicate that ethanol does not merely enhance alpha activity but produces a general EEG slowing (synchronization) dependent both on the dose of ethanol and baseline activity of the EEG. For example, subjects with activated or alert baseline EEG tend to show increased alpha activity after ethanol, whereas subjects starting with high alpha levels show a slowing of the EEG to even lower frequencies (Murphree et al. 1970). Such findings confirm the sedative nature of ethanol since the slow, synchronous EEGs correlate well with increasing drowsiness and subsequent unconsciousness (Engel et al. 1945).

Other evidence for ethanol-induced sedation comes from analysis of the electrical responses evoked by sensory stimulation. Studies of visual (Porjesz and Begleiter 1975; Rhodes et al. 1975; Rosadini et al. 1974), auditory (Krogh et al. 1978; McRandle and Goldstein 1973; Squires et al. 1978; Wolpaw and Henry 1978), and somatosensory (Lewis et al. 1970; Salamy and Williams 1973) evoked responses produce a consistent pattern of results. In all cases ethanol depressed the amplitude of the responses. The late components of these responses (i.e., those with longer latency) were particularly affected, while the earlier components were relatively resistant. A common explanation is that ethanol is most active at synaptic junctions and thus exerts its largest effects on the long-latency (i.e., polysynaptic) components of an evoked response. However, a confounding variable is that the very early components usually reflect subcortical or peripheral nerve activity, while the later components are generated by the cerebral cortex. Thus an alternative explanation proposes a differential sensitivity



ty of various brain regions to the influence of ethanol. This issue is more extensively discussed in the next section.

Another important issue raised in human experiments is the question of the stimulant effects of ethanol. Murphree (1973) demonstrated that a low oral dose (1.0 ml/kg) of ethanol is capable of producing increased power in the beta band of human spontaneous EEG. Interestingly, this same dose also increased alpha activity, suggesting a simultaneous stimulant and sedative effect.

Finally, researchers have demonstrated another interesting influence of ethanol on human electrical activity. Ethanol apparently can reduce the interhemispheric asymmetry of certain evoked responses (Lewis et al. 1970; Porjesz and Begleiter 1975; Rhodes et al. 1975). For example, simple flashes of light normally elicit larger evoked responses in the right occipital cortex than in the corresponding left cortex. This effect is most pronounced in later components of the response. Acute ethanol administration reduced the hemispheric asymmetry essentially by depressing the right hemispheric response down to the level of the left hemisphere (Porjesz and Begleiter 1975). Unfortunately, left hemisphere dominant responses have not been evaluated to test the generality of this phenomenon.

In summary, the literature on human experimentation documents well the sedative nature of ethanol's effects on brain activity. These brain changes appear correlated both with the level of consciousness of the subjects and the rising blood ethanol concentrations. There is also some indication that ethanol can serve as a stimulant at low doses. However, many questions remain unanswered. How are individual neurons affected by ethanol and how do these changes correlate to EEG changes? Are some brain structures particularly sensitive to ethanol? Can ethanol affect neuronal activity when directly applied to neurons? These complex issues can be more effectively addressed by controlled studies in laboratory animals.

### Studies in Laboratory Animals

Carefully controlled studies in rat, rabbit, cat, and monkey have confirmed the basic observations in man outlined above (Dolce and Decker 1972; Hadji-Dimo et al. 1968; Hogans et al. 1961; Horsey and Akert 1953; Mikeska and Klemm 1979; Ohga 1962; Story et al. 1961). These studies have not only reported depressed EEGs following administration of high ethanol concentrations, but several investigators also demonstrated EEG activation or desynchronization at BECs below 50 mg/100 ml (Dolce and Decker 1972; Hadji-Dimo et al. 1968; Horsey and Akert 1953). Other studies of spinal cord reflexes also revealed a biphasic action of ethanol. Monosynaptic and polysynaptic reflexes as well as presynaptic inhibition of these reflexes are all facilitated by very low doses of ethanol but are depressed by higher doses (Kolmodin 1953; Miyahara et al. 1966). Thus the biphasic (stimulant/depressant)

nature of ethanol action appears to be well substantiated by animal studies.

Discrepancies between animal studies in the appearance and severity of changes in the EEG in various brain regions can often be attributed to differences in the route of administration, dose, and rate of infusion. To demonstrate this point, ethanol (1 g/kg) was infused intravenously into cats at a constant rate but in solutions of 10, 20, or 30 percent (Perrin et al. 1974). The EEG changes accompanying these infusion regimens were markedly different. The 30 percent solution slowed the cortical EEG but increased its amplitude. The EEG then progressed to spindle activity, diffuse slow waves, and ultimately complete flattening at the peak blood alcohol level. In contrast, the 10 percent solution produced initial EEG activation and subsequent slowing and spindling, but recovery occurred even prior to the end of infusion when blood alcohol reached its highest level. Within limits, the rate of rise of blood ethanol is more important than its absolute level in determining the intoxicating properties of ethanol. These results also underscore the importance of the parameters of ethanol administration, a methodological consideration not always given proper attention by some alcohol researchers.

### *Neuroanatomic Localization of Ethanol's Acute Effects*

Where in the brain does ethanol exert its primary influences? This issue has received considerable attention. It should be noted at the outset that every region of the brain so far studied has been shown to be affected by ethanol administration in sufficient dosage. To demonstrate which brain regions are particularly sensitive, researchers concentrate on three major aspects of the regional responses to ethanol: magnitude of the effect at a given dose, latency to onset of the effect, and the dose required to produce given effects.

### *Electroencephalographic (EEG) Studies*

The previously described EEG changes following ethanol administration were summarized from scalp recordings in man and direct cortical recordings in animals. Whether these effects are due to direct actions on the cortex or are secondary to alterations in activity of subcortical brain regions has been the subject of much debate. The easiest approach to this question simply involves direct comparisons of EEG recordings from cortical and subcortical loci after ethanol administration. Early reports comparing various brain regions' responses to ethanol were unable to distinguish their pattern and degree of EEG slowing (Erickson and Graham 1973; Horsey and Akert 1953; Story et al. 1961). More recently there have been reports disputing whether cortical or subcortical loci are particularly sensitive (or insensitive) to ethanol's effects (Dolce and Decker 1972; Ohga 1962; Perrin et al. 1974). At this point we must conclude that EEG studies have not

provided good insight into the regional specificity of ethanol's effects on brain. This technique may yet prove to be useful if more careful computer-based analyses are employed.

A confounding factor inherent in the EEG studies is that cortical and subcortical brain regions are not isolated tissues but interact with and modulate each other's activities. Some experimenters have examined ethanol's effect on these patterns of modulation as well as ethanol's direct effect on these structures when they have been surgically disconnected from each other (Akabane et al. 1964; Caspers 1958; Ohga 1962; Sauerland and Harper 1970). From these studies it appears that ethanol can not only depress the interactions of various brain regions but can also continue to influence regional activity even after the disconnection from other brain structures. Such studies suggest that while ethanol can influence the interaction of various brain regions, its effects on spontaneous activity in a given region may be relatively independent of its effects elsewhere in the brain.

### Evoked Potentials (EPs)

A widely used method in the study of ethanol effects on CNS is the evoked potential technique. One advantage of EPs is the ability to simultaneously record both pre- and postsynaptic activity in a variety of brain regions in response to a single stimulus. The stimulus typically involves a sensory cue or direct stimulation of a sensory pathway within the brain. The primary debate of this research area centers on the relative ethanol sensitivity of the cerebral cortex and the brainstem reticular formation. In these studies the cerebral cortex is often subdivided into primary sensory cortex (the first cortical regions to receive sensory information) and sensory association cortex (regions that process the sensory information after it arrives in the cortex). In general, a hierarchy of ethanol sensitivity seems to exist in these various regions.

Using EP techniques, many researchers report that the brainstem reticular formation is relatively more affected by ethanol administration than the primary sensory cortex (DiPerri et al. 1968; Dravid et al. 1963; Himwich et al. 1966; Perrin et al. 1975; Schweigerdt et al. 1965). For a given dose of ethanol, the reticular formation response is earlier, larger, and of longer duration. These results received some corroboration from multi-unit recordings in these same structures (Sutko and Weinberger 1979).

Other reports, however, suggest that the sensory association cortex is even more sensitive to ethanol than the reticular formation. For example, although ethanol reduces the EP amplitude in the primary somatosensory cortex in cats, the somatosensory association cortex exhibits an even greater and more enduring reduction of EP amplitude (DiPerri et al. 1968). Similar findings were observed in monkeys (Hyvarinen et al. 1978). These results have been interpreted as supporting the notion that at least parts of the cortex are primary targets



for ethanol action (DiPerri et al. 1968; Himwich and Callison 1972). This hypothesis is supported further by the finding that ethanol has little effect on brainstem modulation of cortical sensory EPs (Nakai and Domino 1969; Takaori et al. 1966). Unfortunately, few attempts have been made to study other subcortical nuclei, e.g., those that relay sensory information from the periphery to the primary cortical receiving areas. In all cases these nuclei have been shown to be affected less by ethanol than the primary sensory cortex, reticular formation, and sensory association cortex (DiPerri et al. 1968; Nakai and Domino 1969; Squires et al. 1978).

The overall pattern of results from the evoked potential experiments suggests that there may be a consistent hierarchy of ethanol influences on various brain regions. Ethanol appears to be least effective on peripheral nerve activity but seems to exert progressively more influence on the sensory relay nuclei, primary sensory cortex, reticular formation, and sensory association cortex. The action of ethanol on other brain regions has received only minor experimental attention. However, none of these regions has yet been shown to be particularly sensitive to ethanol.

### Unit Studies

While EEG and EP techniques have provided valuable information concerning ethanol actions in the brain, their interpretation is somewhat limited by an inability to identify precisely the neuronal elements contributing to these gross potentials. More fundamentally, an increased amplitude of an EP, for example, cannot be unambiguously interpreted as reflecting a decrease or increase in the underlying neuronal excitability. What such macropotential recording techniques do is provide relevant information on the presence of changes per se in the excitability of large groups of cells, which can serve as a point of departure for more detailed studies involving single and multiple unit (cell) analysis.

A majority of the neurons recorded in the brain are affected by peripheral ethanol administration. However, the response to ethanol varies from structure to structure and even among neurons situated in the same structure. Many cells demonstrate biphasic, dose-dependent response to ethanol (Grupp and Perlanski 1979; Klemm, Dreyfus, and Mayfield 1976). The response of these cells to stimulation in other brain regions is also depressed by the higher dose of ethanol (Folger and Klemm 1978). CNS regions such as the brainstem and spinal cord have shown only decreases of unit activity in response to ethanol (Eidelberg et al. 1971; Eidelberg and Wooley 1970; Pohorecky and Brick 1977; Sutko and Weinberger 1979). A few brain regions contain some neurons that are excited by ethanol while neighboring neurons are depressed (Eidelberg et al. 1971; Mikeska and Klemm 1979; Wayner et al. 1973). It is not clear how these cells differ in ways other than their sensitivity to ethanol.



Only one or two studies have compared extensively the effects of ethanol on the spontaneous EEG and multiple unit activity of a wide variety of brain regions. These studies, however, reveal that changes in multiple unit activity seem to be poorly correlated with the EEG. On the basis of the unit results, brain regions are grouped as slow responding areas or fast responding areas (Klemm et al. 1976; Klemm and Stevens 1974). One conclusion from these data is that the sensitive (i.e., fast responding) regions tend to be in the cerebral cortex and reticular formation (reminiscent of the EP results). A more careful quantitative analysis is required to substantiate these findings.

One unresolved issue pertaining to all of the above studies concerns whether ethanol itself acts directly at the recording site. Two problems arise here: First, does ethanol or some metabolite produce the effect? Second, is ethanol acting primarily in some other region (e.g., the periphery) and secondarily affecting the region being monitored? Despite many attempts to control peripheral factors such as respiration and blood pressure, and careful correlations with blood ethanol concentrations, these questions remain unresolved. One recent approach to these problems is the iontophoretic application of minute quantities of ethanol directly onto the recorded cells. In the cortex, there is apparently little effect of ethanol on spontaneous unit activity (Lake et al. 1973). When neurons do respond, they tend to show enhanced activity (Wayner et al. 1975). Other regions, however, are depressed by iontophoretically applied ethanol (Siggins and French 1979). A unique study employing cultures of the cerebellum (another brain region) revealed that ethanol produced a biphasic dose-dependent effect on neuronal spontaneous activity (Seil et al. 1977). A depressive influence was also observed on EPs. Curiously, the lowest effective dose was considerably larger than a similarly acting dose in intact animals. Although these few studies should be considered preliminary, the general pattern of results cautions us to consider that the direct effects of ethanol on the nervous system may be other than what is typically described to result from systemic ethanol administration.

## Conclusions

The search for the "primary" site of ethanol action still continues. Many of the past difficulties can be attributed to the reliance on measures of relative magnitude of effects, such as the degree of EEG slowing, the amplitude of an EP, the latency of an EP, or the percentage of neurons activated or depressed. Too many other regional differences exist to be able to compare regional variations in response to ethanol as determined by these measures. Fortunately, more emphasis has been placed recently on considerations of dose-response curves and the latency to onset of particular effects. The study by Sutko and Weinberger (1979) is exemplary in this regard.

Other considerations remain. As discussed above, to what extent does ethanol act directly on the brain? For instance, regional differ-

ences in response to ethanol may merely reflect changes in regional cerebral blood flow (Kalant 1975). Alternatively, metabolites of ethanol such as acetaldehyde or tetrahydropapaveroline may be the active agents. But the final caveat is that there may well be no "primary" site of action. All parts of the nervous system studied so far have been shown to be susceptible to ethanol's influence. There is still no convincing evidence that an ethanol-related alteration of one region's activity is subordinate to a change in some other region. Finally, while it still remains likely that some regions are more sensitive to ethanol's effects, we have no evidence that they correlate with those areas responsible for its intoxicating actions (Killam 1962).

Although we are not sure where ethanol exerts its effects, nonetheless we know a great deal about what effect ethanol, acutely administered, produces in the brain, whether directly or indirectly. First, ethanol typically exerts a biphasic (stimulant/depressant) influence on spontaneous brain activity. This effect is widespread in the CNS and is well correlated with both the dose and rate of administration as well as the resulting blood ethanol concentration. Second, ethanol can affect EPs, particularly the later components. One interpretation of such findings is that ethanol exerts most of its effects at synapses, so that polysynaptic pathways (contributing to the late components of EPs) demonstrate the greatest responses to ethanol. The ubiquitous nature of the phenomenon indicates that this hypothesis is worth pursuing. Alternatively, as mentioned above, it may be that some of these regions are particularly sensitive to ethanol. The available data are inconclusive on this point. Clearly more research, utilizing more sophisticated EEG and single unit analyses, is required to clarify this issue.

### ***Tolerance and Physical Dependence***

The behavioral abnormalities observed during the alcohol withdrawal reaction are believed to reflect the release of a latent state of neural hyperexcitability developing as a result of continuous exposure to ethanol (Kalant et al. 1971). The development of this neural hyperexcitability has been proposed to result from a variety of cellular adaptive mechanisms (Collier 1965; Goldstein and Goldstein 1968; Jaffe and Sharpless 1965; Martin 1965). The presence of this neural hyperexcitability has largely been inferred from behavioral observations including reductions in threshold and/or response amplitude of startle responses (Gibbins et al. 1971; Pohorecky et al. 1976) or convulsions elicited by chemical (Hunt 1973; McQuarrie and Fingl 1958) or auditory (Freund and Walker 1971b) stimuli.

The alcohol withdrawal syndrome in man is characterized by several symptoms (Victor and Adams 1953). One group of symptoms includes tremor, hallucinations, insomnia, anorexia, irritability, and agitation. These typically reach a peak intensity 24 hours after alcohol absti-

nence. Convulsive seizures may occur singly or in short bursts 7-48 hours after withdrawal and are most often "generalized" as opposed to "focal" seizures (Avaloff 1979). A final group of symptoms, collectively referred to as delirium tremens, reaches its greatest intensity 72-96 hours after withdrawal. On the basis of this evidence, two major phases of the withdrawal syndrome have been proposed (Wolfe and Victor 1971): a minor withdrawal syndrome including tremors, hallucinations, and convulsions and a major withdrawal syndrome consisting of delirium tremens. Qualitatively similar results have now been observed in a variety of laboratory animals including mice, rats, cats, and monkeys (Freund 1975).

Relatively few investigators have examined EEG activity in man during the alcohol withdrawal reaction, perhaps due to inherent methodological difficulties (Begleiter and Platz 1972). In a now classic investigation Wikler et al. (1956) studied three subjects maintained on variable doses of alcohol for 48 to 55 days. Ethanol initially produced a diffuse slowing of the EEG consistent with its acute effect on the EEG of man. The diffuse slowing persisted during the alcoholization period but to a lesser degree. This apparent tolerance was not always correlated with associated behavioral signs of tolerance. The EEG effects of ethanol tolerance have been reported in cats (Perrin et al. 1975). The effects of ethanol tolerance on rat auditory brainstem EPs (Chu et al. 1978) have also been reported. Upon abrupt ethanol withdrawal (Wikler et al. 1956) the EEG eventually develops abnormalities, consisting of transient epileptiform spiking and sharp waves of paroxysmal discharges, reaching peak intensity 15-19 hours after withdrawal. This transient cortical EEG dysrhythmia was characterized as unspectacular and a motor seizure was observed in one patient in the absence of gross EEG abnormalities.

Direct EEG recordings from cortical and subcortical sites during alcohol withdrawal have been reported in mice (Maxson and Sze 1976; Walker and Zornetzer 1974), rats (Hunter et al. 1978; Hunter and Walker 1978, 1980), and cats (Guerrero-Figueroa et al. 1970; Perrin et al. 1975). These studies indicate that the alcohol withdrawal reaction is accompanied by the presence of epileptiform activity diffusely organized in both cortical and subcortical loci. These epileptiform abnormalities characteristically begin with the appearance of transient epileptiform spike activity, which then increases in amplitude and frequency during the zenith of the withdrawal reaction. This progressive increase in epileptiform spike activity often culminates in the appearance of complex paroxysmal epileptiform events, including sustained seizure discharge terminating in overt motor seizures.

The progressive and diffuse alteration in the excitability of cortical and subcortical brain sites during alcohol withdrawal is confirmed in studies of somatosensory, visual, and auditory evoked responses in man (Begleiter et al. 1974), rats (Begleiter and Coltrera 1975; Chu et al. 1978), and monkeys (Begleiter et al. 1980). In this series, alcohol withdrawal was accompanied by either an increased amplitude of the



specific sensory EP or decreased latency, both of which indicate altered CNS responsiveness. In all cases, significantly greater effects were observed in the late components of the EP, a finding reminiscent of ethanol's acute effects. These results support the view that alcohol withdrawal is accompanied by a diffuse alteration in neural excitability. Similar results have been recently reported for EPs induced by electrical stimulation of the amygdala (Hunter and Walker 1980).

A major question emerging from these results is the anatomical extent of the changes in neural excitability during the withdrawal reaction. It is now clear that the genesis of this altered neural excitability cannot be localized to any single area of brain. However, neural hyperexcitability is not manifested in every brain region. For example, studies of the late component of the visual evoked response during alcohol withdrawal reveal significant increases in amplitude in diverse brain areas including reticular formation, hippocampus, frontal, and parietal cortex, but no significant change in lateral geniculate, pulvinar, and visual cortex. A comparable approach quantified epileptiform spike activity across widespread brain regions during alcohol withdrawal in rats (Hunter et al. 1978; Hunter and Walker 1978, 1980). Brain regions were categorized into: (1) primary sites, where epileptiform activity develops early and with greatest intensity, (2) secondary sites, where spike activity develops more slowly but reaches levels indistinguishable from primary sites, and (3) tertiary sites, where spike activity is significantly lower throughout the withdrawal reaction (Hunter and Walker 1980). The data indicate that the genesis of the specific behavioral symptoms of the alcohol withdrawal syndrome is closely associated with the development of altered neural excitability localized to specific brain sites. Further research will be required to assess the nature of these brain sites, the types of biochemical and physiological adaptive processes occurring at these sites during prolonged ethanol exposure, and how abnormal bioelectric activity is eventually manifested in the symptoms of the alcohol withdrawal syndrome.

Neurophysiological studies of the development of tolerance and physical dependence most recently have been extended to analysis of single unit activity. Rogers et al. (1980) found that single unit responses of Purkinje cells in the cerebellum to activation of climbing fibers (a powerful excitatory input) were enhanced during acute ethanol intoxication. This ethanol-induced enhancement was absent in animals exposed to ethanol for 11-14 days. Beginning 3 hours and extending 32 hours after ethanol withdrawal, Purkinje cell responses to climbing fiber activation progressively decreased. Since the cerebellum is known to inhibit forebrain epileptiform activity powerfully, the observed decrease in Purkinje cell responsiveness may have important implications for the development of epileptiform activity during ethanol withdrawal (Hunter and Walker 1978). Moreover, Rogers et al. (1980) suggest that the pattern of changes may reflect physiological correlates of ethanol intoxication, tolerance, and physical dependence. This promising ap-



proach should provide future insight into the physiological mechanisms underlying tolerance and physical dependence on ethanol.

## ***The Effects of Ethanol on Sleep***

Sleep patterns for normal adults, as defined largely by EEG criteria for sleep stages, are well characterized. As mentioned earlier, the two major classifications of the sleeping EEG are slow wave sleep (SWS) and rapid eye movement (REM) sleep. Normally, the patterning of sleep, or the cyclical and dynamic interplay between the various sleep stages, follows reasonably predictable and stable rules. Drugs and other factors are capable of altering these normally stable patterns. Studies investigating the effects of ethanol on the EEG during sleep have asked a number of questions: (1) What are the effects on sleep of an acute dose of ethanol in nonalcoholics? (2) How do the sleep rhythms of chronic alcoholics differ from those of normal individuals? (3) What happens to the sleep rhythms of alcoholics during and after withdrawal? (4) What are the effects of acute alcohol administration on "recovered" alcoholics? Let us consider each of these questions.

### ***The Effects of Acute Ethanol on Sleep in Nonalcoholics***

Alcohol consumption prior to sleep in the normal individual leads to a brisk sleep onset due to the sedative effect of ethanol. EEG recordings indicate further that normal sleep patterns are disturbed. SWS is significantly elevated during the first half of the night with an associated decrease in REM sleep. During the second half of the night there is an apparent compensatory REM rebound coupled with a higher than normal level of sleep disturbances (Knowles et al. 1968; Yules et al. 1966).

### ***The Sleep Rhythms of Chronic Alcoholics Compared to Those of Normals***

As tolerance to and physical dependence on ethanol develop with continued drinking, a higher affective dose of ethanol is required to obtain a sedative effect (Rundell et al. 1977). Similarly, the initial increase in SWS and associated decrease in REM sleep tend to disappear with continued drinking. A somewhat more normalized composition of the sleep rhythms may return. The patterns of sleep in alcoholics are highly variable and individualized. Depending on baseline levels of SWS in a particular individual, a given dose of ethanol prior to sleep onset could cause a decrease, no change, or an increase in baseline SWS levels (Gross and Hastey 1975).

### *Sleep Rhythms in Alcoholics During Abstinence*

The abstinent alcoholic manifests the most dramatic alteration of sleep patterns. Initially, during alcohol withdrawal, sleep is characterized by multiple awakenings, sleep stage fragmentation, and, in some individuals, a REM sleep rebound. Some investigators have reported that disturbed sleep patterns in abstinent alcoholics normalize after only 5 to 8 days of abstinence (Allen et al. 1971). Most workers, however, suggest that normalization requires considerably longer. For example, Wagman and Allen (1975) reported that SWS was markedly suppressed for up to 3.5 weeks after cessation of drinking. Remarkably, they found that in some subjects complete SWS recovery required 1 to 4 years of abstinence. Similarly, Adamson and Burdick (1973) reported reduced components of SWS coupled with frequent interruptions of REM episodes and an abnormally high number of sleep stage changes in previous alcoholics abstinent for 1 to 2 years. It appears that during the period of abstinence and prior to complete normalization (if indeed it even occurs), abstinent alcoholics have elevated stage 1 sleep, depressed stage 4 sleep, and more frequent REM episodes coupled with frequent REM disruptions (Gross et al. 1973; Johnson et al. 1970; Lester et al. 1976; Rundell et al. 1977; Wagman and Allen 1975; Zarcone et al. 1977). Collectively, these findings suggest that the abstinent alcoholic suffers from an impaired organization of a basic physiological cycle.

Recovery to normal of these altered sleep rhythms in an abstinent alcoholic may be a useful prognosticator of total recovery from alcoholism. Allen et al. (1971) suggest that persistent decreased SWS in abstinent alcoholics may indicate continued tolerance and dependence upon ethanol. Gross and associates (Gross and Best 1975; Gross and Hastey 1975; Gross et al. 1974) similarly suggest that persistent decreased SWS may correlate with a subacute and perhaps even chronic subclinical withdrawal syndrome. Accordingly, these workers speculate that the persistent decline in SWS in an abstinent alcoholic may indicate a "silent" carryover of the addictive mechanism.

### *The Effects of Ethanol Administration on the "Recovered" Alcoholic*

Studies of abstinent alcoholics who resume drinking suggest that the rate of reacquisition of tolerance is negatively correlated with the percentage baseline level of SWS (Allen et al. 1971; Gross and Best 1975; Wagman et al. 1978). In other words, the greater the decrease in SWS during the abstinent period the more rapidly tolerance was reacquired. These data support Kalant's (1973) suggestion of a "carryover" phenomenon of some residual effects of functional tolerance and physical dependence that result in a more rapid reacquisition of tolerance and physical dependence on reexposure to alcohol. EGG measures of SWS abnormalities appear to be a clinically useful prognosticator of "carryover."

In summary, EEG measures of altered sleep rhythms during and after periods of alcoholization can be useful not only in diagnosing the severity of dependence but perhaps also in determining a prognosis for recovery.

### ***The Neurotoxicity of Chronic Alcohol Abuse: Anatomical, Electrophysiological, and Behavioral Correlates***

Chronic alcoholism is associated with profound alterations in central nervous system structure and function (Begleiter and Platz 1972; Brion 1969; Courville 1966; Dreyfus 1974; Freund 1973; Parsons 1977; Victor et al. 1971). The multifaceted nature of alcoholism, and the inherent difficulties involved in experimental control in human studies, make causal relationships between alcohol exposure per se and the associated functional and structural CNS abnormalities difficult to establish. The methodological difficulties in identifying electrophysiological abnormalities (such as distinctive alterations in EEG and evoked potentials) attributed to chronic alcoholism have been reviewed by Begleiter and Platz (1972) and Parsons (1977). These authors note logical problems and pitfalls in attributing neuroanatomical and neuropsychological abnormalities of chronic alcoholics solely to the effects of alcohol. As pointed out, some of the problems in interpreting results arise because many other variables such as aging, abuse of other drugs, head trauma, other disease processes, and malnutrition often coexist with alcoholism. These variables could also result in alterations in brain structure and function. In addition, other methodological problems arise because of sampling bias, unavailability of appropriate control groups, variability in duration, quantity and pattern of alcohol consumption, length of abstinence, and medication at the time of testing.

Despite problems of interpretation, a consistent pattern of results is beginning to emerge. The purpose here is to review selectively the evidence that residual neurophysiological abnormalities are associated with brain changes resulting from chronic alcohol consumption. The unique opportunity afforded by the use of an animal model in discovering the relationship between chronic alcohol ingestion and residual alterations in brain structure and function will be discussed.

#### ***EEG and EP Indexes of Alcohol Brain Damage***

Visual inspection of the EEG of a chronic alcoholic typically reveals increased low-frequency components (1-7 Hz) (Artentzen and Sindrup 1963; Bennett 1960; Bennett et al. 1956, 1960; Greenblatt et al. 1944), as well as increased high-frequency components (13-30 Hz) (Bennett et al. 1960; Funkenhouser et al. 1953; Lester and Edwards 1966). More recently, investigators using computerized analysis of EEG (power



spectral density analysis) have confirmed earlier reports of an increase in both low-frequency and high-frequency EEG bands associated with chronic alcoholism (Coger et al. 1978, 1979). It has also been reported that there are no consistent EEG abnormalities in chronic alcoholics (Dyken et al. 1961), especially those below the age of 60 (Newman 1978).

So far, relatively few studies have used evoked EPs to assess brain function in abstinent alcoholic patients (Beck et al. 1979; Bergamasco and Gandiglio 1965; Pfefferbaum et al. 1979; Salamy et al. 1980). Bergamasco and Gandiglio (1965) investigated somatosensory evoked potentials (stimulation of the ulnar nerve) recorded from scalp electrodes over the somatosensory cortex. These authors reported that the latencies of several components of the EPs in alcoholic patients were longer than in normal subjects. It is generally thought that the short latency components of sensory EPs represent the activity of specific sensory pathways and therefore correspond to the 'sensory-receiving' process, while later components of the EP are related to the "higher order" processes such as attention and information processing (Beck 1975; Kutas et al. 1977).

Three recent studies compared sensory EPs of abstinent chronic alcoholics and nonalcoholic controls (Beck et al. 1979; Pfefferbaum et al. 1979; Salamy et al. 1980). Pfefferbaum et al. (1979) studied 10 abstinent chronic alcoholics (10 years or more of drinking) and 10 age- and sex-matched controls. Auditory (speech sounds or tones) EPs recorded from scalp leads were compared in the two groups. The early EP components did not differ in amplitude or latency between the two groups. However, the latency of the major late component was significantly longer in the alcoholic group, presumably reflecting a deficit in cognitive processing in alcoholics (Beck 1975). Similar results were found by Beck et al. (1979), who studied the visual evoked responses of young abstinent chronic alcoholics (mean age 33 years) as compared to young normals (mean age 31 years). These investigators also found no differences between alcoholics and normals in the latency and amplitude of the early components of the visual EP, but the late-wave components were found to be reliably smaller and of longer latency in the alcoholic group. In contrast, Salamy et al. (1980) recently reported that the early components of auditory EPs were reliably smaller in amplitude in abstinent chronic alcoholics than in normal controls. Subjects were tested on two occasions separated by 20 days. On the first test the mean amplitude of the alcoholics' EPs was smaller than that of controls in both parietal and frontal regions. However, on the second test the alcoholics' parietal responses had improved, whereas the frontal responses remained significantly smaller than those of controls.

In summary, there appears to be accumulating evidence that chronic alcohol ingestion is associated with persistent alteration in EEG patterns and in certain characteristics of sensory evoked potentials recorded from scalp electrodes in man. One important question, and

one for which there is a paucity of available data, is how these persistent neurophysiological alterations observed in chronic alcoholics are related to other indexes of alcohol-related brain damage such as cognitive impairment and brain pathology.

### *Anatomical Indexes of Alcoholic Brain Damage*

Post mortem studies of brains of chronic alcoholics who have suffered from Wernicke's disease and/or Korsakoff's psychosis report neuropathological alterations in a wide variety of brain regions (Brion 1969; Dreyfus 1974; Victor et al. 1971). Brion (1969) concluded that damage to the mammillary bodies and/or the hippocampal complex is consistently associated with severe learning and memory loss in alcoholic Korsakoff patients, while Victor et al. (1971) place more importance on the dorsomedial thalamus as a neuroanatomical correlate of impaired memory. Other post mortem neuropathological studies of brains from chronic alcoholics emphasized the presence of atrophy of the cerebral cortex (Courville 1966; Lynch 1960; Neubuerger 1957) or neuronal loss in the hippocampus (McLardy 1973a, b).

A number of neuroradiological studies using pneumoencephalographic (PEG) measurements of brain atrophy in chronic alcoholic patients report a high prevalence of brain atrophy (50-100 percent) as measured by increased size of brain ventricles (Brewer and Perrett 1971; Carlsson et al. 1970; Castro 1969; Haug 1968; Horvath 1975; Tumarkin et al. 1955). Because of the risk and discomfort associated with the PEG, only individuals with sufficient medical reason are chosen for this procedure. Thus, the majority of the PEG studies cited are based on data from alcoholic individuals selected for dementia or suspected neurological disorders and "normal" controls were obviously not available for comparison. Because of the necessarily biased selection procedures and the lack of neurologically normal control groups for comparison, it is possible that the true prevalence of brain damage associated with alcoholism as such could be overestimated in PEG studies (Hill in press).

The advent of computerized axial tomography (CAT) provides an opportunity to learn more about the relationship between alcoholism and structural alterations of the brain than has been previously possible. The CAT scan is a noninvasive technique that can be used in subjects who would not normally be referred for PEG. The method provides quantifiable information concerning ventricular size and cerebral atrophy. Since the introduction of the CAT there have been a number of reports of enlarged ventricles and/or cortical atrophy (enlarged cortical sulci) in alcoholics as measured by CAT scan (Avdaloff 1979; Carlen et al. 1978; Epstein et al. 1977; Fox et al. 1976; Hill in press; Lee et al. 1979). Curiously, the one prospective study using a normal control group for comparison (Hill in press) found no evidence of significant ventricular enlargement in the alcoholic group as compared to normal

controls. The results of this study, however, do suggest that cortical sulci are enlarged in the alcoholic group.

In summary, there is ample evidence that chronic alcoholism is associated with brain damage. There are, however, a number of important questions remaining to be answered: (1) Is subcortical (Brion 1969; Dreyfus 1974; McLardy 1973a, b; Victor et al. 1971) or cortical (Carlen et al. 1978; Courville 1966; Epstein et al. 1977; Lynch 1960) damage more directly related to cognitive deficits associated with alcoholism (Parsons 1977)? (2) Are some individuals more susceptible to alcohol-induced brain damage than others? (3) What is the relationship between duration, amount, and pattern of alcohol intake and associated brain damage?

*Correlations Between Neurophysiological, Neuropathological, and Neuropsychological Measures of Brain Damage Associated with Alcoholism*

Few experiments have been reported to date in which neurophysiological, psychometric, and neuropathological measures are collected in the same population of abstinent chronic alcoholics and controls. With the present availability of computer-assisted EEG and evoked potential data collection and analysis, noninvasive techniques to evaluate brain atrophy (CAT), and improved neuropsychological test batteries, the data base should soon increase.

Available data concerning the interrelationship among these three indexes of brain damage are not entirely consistent. These inconsistencies are at least partially the result of the previously described methodological and interpretational difficulties inherent in these experiments. EEG abnormalities in chronic alcoholics are reported to be more severe in patients with the most severe cerebral atrophy (Bennett 1960). Victor et al. (1971) reported, conversely, that Wernicke-Korsakoff patients with severe neuropathological and cognitive deficits often had entirely normal cortical EEGs. More recently, Newman (1978) found that chronic alcoholics under 60 years of age may have a normal EEG (visual inspection only) despite the presence of cerebral cortical atrophy assessed by CAT, while in alcoholics over 60 years of age there was a direct relationship between cerebral cortical atrophy and decreased background frequency of the EEG.

More consistent results have been obtained in the few studies attempting to determine the relationship between electrophysiological and neuropsychological deficits of chronic alcoholics (Coger et al. 1978; Funkenhouser et al. 1953; Lester and Edwards 1966). In the most recent of these studies (Coger et al. 1978), EEGs were recorded in two groups of alcoholics who had scored at opposite extremes on the Shipley Institute of Living Scale. The groups were otherwise matched for age and drinking history variables and their EEGs were compared to age-matched control subjects by power spectral density analysis. Both alcoholic groups had increased low (1-7 Hz) and high (14-30 Hz)



frequency EEG components compared to controls. In addition, the EEGs of the more severely impaired alcoholics contained significantly more high-frequency components than either of the other two groups, particularly in recordings from frontal lobe electrodes. These results suggest the possibility that increased high-frequency components of the EEGs of chronic alcoholics correlate well with the extent of the neuropsychological deficit.

There is disagreement on the relationship between the extent of cerebral atrophy and the extent of neuropsychological deficit. Two recent experiments (Hill in press; Lee et al. 1979) failed to find a significant correlation between the degree of intellectual impairment (as measured by psychometric testing) and the extent of cerebral atrophy (as measured by CAT) in chronic alcoholics. An earlier study (Brewer and Perrett 1971) suggested that a significant relationship was evident between morphological (PEG) and psychometric indexes of brain damage in chronic alcoholics.

There is ample evidence that chronic alcoholism is associated with brain neuropathology (as measured by PEG, CAT, or post mortem assessment), persistent neurophysiological alterations (EEG and EP measures), and cognitive impairment (psychometric testing). The direct relationship among these three indexes of alcohol-induced brain damage in the same individuals is not yet established. The reasons for the lack of consistent correlations among these three indexes of alcoholic brain damage is probably the result of a number of factors including problems of methodology and interpretation inherent to these types of experiments (Begleiter and Platz 1972; Freund 1973; Parsons 1977). It is also possible that the persistent cognitive deficits and neurophysiological alterations associated with alcoholism are more directly related to noncortical brain damage (Brion 1969; McLardy 1973a, b; Victor et al. 1971) which may not be assessed adequately by noninvasive techniques such as PEG, CAT, or surface EEG or EP recordings.

### *Animal Studies of Alcohol-Induced Neurotoxicity*

Animal studies can provide vitally important information about the effect of chronic alcohol consumption on brain structures and function. Variables such as age, nutrition, and heredity can be held constant, allowing the effects of ethanol to be assessed without the problems of interpretation inherent in human clinical studies. Also, invasive techniques can be used in animals (e.g., direct electrophysiological, histological, and neurochemical measurements of brain tissue) that are not generally available for use in man.

During the last 10 years there has been considerable interest in developing and using animal models of chronic alcohol toxicity. A number of experiments demonstrate that chronic alcohol exposure in animals results in a permanent behavioral deficit in a variety of tests of learning, memory, and performance (Bond and DiGiusto 1976; DeNoble

and Begleiter 1979; Fehr et al. 1976; Freund 1970; Freund and Walker 1971a; MacDonall and Marcucella 1978; Smith et al. 1979; Sotzing and Brown 1976; Walker and Freund 1971; Walker and Hunter 1978). In these experiments, the enduring behavioral deficits were attributed solely to the effects of chronic ethanol exposure, since all other variables were held constant in both ethanol-treated and control groups by the rigid experimental control possible in animal experiments. The ethanol-induced learning impairment is apparently permanent since the deficit is present unabated even after an ethanol-free period of 5 months (Freund and Walker 1971a). The extent of the behavioral deficit also depends on the duration of the ethanol exposure. Shuttle-box avoidance learning, for example, is unaffected by 6 weeks of ethanol ingestion, but is increasingly impaired as the duration of previous ethanol consumption is increased to 3, 5, or 7 months (Freund and Walker 1971a). Rats exposed chronically to ethanol for 5 months are subsequently deficient in short-term memory in much the same fashion as chronic alcoholic patients (Walker and Hunter 1978).

It is likely that the functional impairments observed in alcoholic patients and ethanol-exposed animals are related to specific alterations in the neurophysiological and/or neuroanatomical integrity of the brain. Anatomical and neurophysiological investigations of alcoholic patients are necessarily limited to rather gross, noninvasive measures of brain structure and physiology as previously discussed. Animal studies in which quantitative neurohistological and neurophysiological techniques are used to assess the neurotoxic effects of ethanol on specific populations of neurons, and on specific neural circuits, should be of significant value in determining the relationship between altered nervous system structure and function associated with alcohol abuse.

To date, there have been no published reports concerning the measurement of enduring neurophysiological alterations in animals following prolonged ethanol exposure. However, quantitative neurohistological techniques are now being used to investigate the effect of prolonged ethanol consumption on the structural integrity of the brain (Riley and Walker 1978; Walker, Barnes, Riley, Hunter, and Zornetzer 1980). In these experiments, good nutrition did not protect the brains of ethanol-consuming animals from neuropathological alterations. More specifically, several months of ethanol consumption resulted in structural alteration of dendrites and neuronal loss in the hippocampus and cerebellum of mice and rats (Riley and Walker 1978; Walker, Barnes, Zornetzer, Hunter, and Kubanis 1980). These results suggest that the hippocampus and cerebellum may be especially sensitive to the neurotoxic effects of ethanol. Future research relating neurophysiological and neurohistological measures with the degree of behavioral deficit in the same set of ethanol-treated rats will clarify the relationship among these variables.

## Summary and Conclusions

A variety of neurophysiological methods useful in assessing the effects of acute and chronic ethanol administration on the nervous system have been described. Data from both human and nonhuman experiments indicate that these methods can be used effectively to determine the severity and extent of alcohol-induced changes in electrical activity. For example, long-term persistent changes in the organization of human EEG rhythms were described for abstinent chronic alcoholics. In some cases, such changes are reported to endure for years.

Research findings from animal models of alcoholism suggest further that specific brain regions might be differentially susceptible to alcohol-associated pathology. Neurophysiological indexes of altered patterns of cellular and aggregate electrical activity from these regions will serve as an essential physiological link between post mortem analyses of altered structure and behavioral abnormalities associated with altered brain function.

To date, research in the area of neurophysiology and alcoholism has focused either on the acute, the chronic, or the physical dependence aspects of alcohol exposure. Few, if any, studies have attempted to relate neurophysiological data obtained from one research aspect to another. This is an area of important future concern. Specific questions need to be addressed: Are the brain regions affected by acute ethanol exposure the same ones affected by long-term exposure? Are acute and/or chronic effects of ethanol due to its primary actions or its secondary actions? To what extent are the neuropathological consequences of long-term ethanol exposure a result of complications from prior withdrawal episodes rather than direct toxic effects of ethanol?

The ultimate research and clinical benefits to be derived from these neurophysiological methods are considerable. One tangible example is the likelihood that in the near future, EEG recordings might serve as a reliable indicator of long-term carryover of tolerance following a period of alcohol abstinence. Such quantitative data could serve as an important adjunct to conventional methods used in the diagnosis and treatment of chronic alcoholism.

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## **Chapter 5**





# Effects of Alcohol on Liver and Blood Lipids and Lipoproteins

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## Abstract

Excessive alcohol intake results in derangements of hepatic and blood lipid and lipoprotein metabolism, resulting in profound abnormalities in the concentration and composition of lipids and lipoproteins in the liver and in the circulation. These changes are related in part to direct consequences of the metabolism of alcohol by the hepatocyte, to alterations in hepatocyte function induced by alcohol, and also to alterations in lipid metabolism in peripheral tissues. As a result of these metabolic changes, hepatocellular injury (called alcoholic hepatitis), excessive triglyceride accumulation in the liver (fatty liver), and sometimes dramatic increases in the levels of fat (triglyceride) in the blood are produced. In addition to the toxic effects of excessive alcohol, there is recent data to indicate that alcohol in moderate amounts can elevate the levels of cholesterol contained in the high density lipoprotein fraction of blood. Since recent epidemiological studies indicate that elevations of high density lipoprotein-cholesterol concentration are associated with a decreased risk of the development of atherosclerotic vascular disease, it is possible that alcohol in modest amounts may provide beneficial effects related directly to changes in lipoprotein concentration. It is the purpose of this chapter to review recent knowledge concerning the mechanisms by which ethanol can produce changes in liver and blood lipid and lipoprotein metabolism and to discuss various viewpoints concerning the pathophysiological mechanisms which lead to such abnormalities. Clinical sequelae of these metabolic derangements are reviewed, emphasizing changes in hepatocellular lipid metabolism and emphasizing the striking alterations in the composition and concentration of blood lipids and lipoproteins which accompany alcohol-induced liver injury. Furthermore, possible ameliorating effects of alcohol on blood high density lipoprotein-cholesterol are discussed, emphasizing possible physiological mechanisms by which alcohol may induce such changes. Finally, the chapter concludes with a brief discussion of what are thought to be future directions for important research concerning the effects of alcohol on liver function and lipid metabolism.

## ***Introduction***

Excessive alcohol ingestion can produce repeated episodes of liver cell injury. After many years, these injuries may lead to the irreversible changes in the liver called cirrhosis. Although individuals vary greatly in their susceptibility to alcohol toxicity, liver cell injury (also called hepatocellular necrosis) is usually preceded by the daily consumption of large quantities of alcohol over a relatively long period of time.

Acute ethanol-induced hepatocellular necrosis results in a wide variety of clinical symptoms ranging from relatively asymptomatic enlargement of the liver to the development of massive fatty infiltration of the liver and rapid (fulminant) hepatic failure (Galambos 1972). However, alcohol-induced liver toxicity usually consists of discrete episodes of hepatocellular injury associated with fatty liver of varying extent (Sabesin, Hawkins, Bertram, Mann, and Peace 1978). With time the injurious process evolves into a chronic form of hepatic dysfunction characterized microscopically by liver cell regeneration, chronic inflammation, and architectural distortion secondary to proliferation of fibrous tissue (collagen). The process culminates in the clinical and pathological features called cirrhosis and eventual failure of liver function (Harinasuta and Zimmerman 1971).

It is noteworthy that each phase of alcohol-induced liver injury shows abnormalities, sometimes profound ones, in the concentration and composition of blood fats (lipids) and lipoproteins, the molecules that transport fat in the blood. The changes in the blood fats range from modest to enormous increases in triglycerides (the major fat in blood) and cholesterol to complex derangements in blood plasma lipoprotein metabolism. These abnormalities are frequently associated with fatty infiltration of the liver and reflect the importance of the liver in many aspects of lipid and lipoprotein synthesis and metabolism (Sabesin et al. 1979, 1980).

One of the most striking and most frequent pathological consequences of acute alcoholic liver injury is the accumulation of large quantities of triglycerides in the liver cells. The deposition of fat in the hepatocytes causes enlargement of the liver and interference with hepatic function. Despite intensive studies, the exact pathogenesis of alcoholic-induced fatty liver is still uncertain (Baraona and Lieber 1979; Lieber and Rubin 1968a; Scheig 1970). Metabolic alterations occurring after ethanol ingestion, which may cause triglyceride accumulation in the liver, include increased mobilization of fatty acids from fat depots (adipose tissues), increased uptake of fatty acids from the blood by the liver, increased hepatic fatty acid synthesis, decreased fatty acid oxidation, increased esterification of fatty acids to triglycerides, and decreased secretion of triglycerides from the liver (Isselbacher and Greenberger 1964). The accumulation of fat may reflect an imbalance between excessive triglyceride synthesis and the ability of the liver to



assemble and secrete the triglycerides in the form of the lipid-protein complexes called lipoproteins.

It is characteristic of acute alcoholic fatty liver that plasma triglycerides are elevated, suggesting an increased hepatic production and release of triglycerides (Baraona and Lieber 1979). The development of elevated triglycerides in the blood (hypertriglyceridemia) may be very profound, producing milky-appearing (lactescent) blood.

Striking abnormalities in plasma lipoprotein concentration, composition, and structure are also found in patients with so-called alcoholic hepatitis (Sabesin, Hawkins, Kuiken, and Ragland 1977). The derangements of lipid and lipoprotein metabolism reflect the effects of ethanol on peripheral and hepatic lipid metabolism and the effects of alcohol on the function of the liver cells. These alterations are secondary to complex abnormalities in the hepatic biosynthesis and secretion of plasma lipoproteins and in their catabolism in the blood (Sabesin et al. 1980). Although the defects in lipoprotein metabolism are usually reversible with abstinence from alcohol, provided liver function returns to normal, they indicate serious effects of alcohol on the liver that can result in cirrhosis and eventual hepatic insufficiency.

In addition to the obvious deleterious effects of excessive alcohol ingestion on liver and blood lipids and lipoproteins, new and potentially very important information suggests that ethanol in moderate quantities may increase the levels of cholesterol in a class of lipoproteins called high density lipoproteins (HDL). Recent epidemiological evidence indicates that high concentrations of cholesterol in HDL (HDL-C) are inversely related to the incidence of coronary heart disease (Castelli et al. 1977; Gordon et al. 1977; Hartung et al. 1980; Miller and Miller 1975). In other words, high HDL-C protects against the development of coronary heart disease. Alcohol, by mechanisms to be discussed thoroughly later, appears to elevate HDL-C. Thus a new area of alcohol research is evolving that may have important implications in relationship to heart disease.

The purpose of this chapter is to discuss the various ways alcohol can produce abnormalities in liver and blood lipids and lipoproteins. The metabolism of alcohol by the liver, the postulated pathogenesis of alcohol-induced hepatocellular injury, and the relationship of alcohol and nutritional status to liver disease have been reviewed extensively (Baraona and Lieber 1979; Hawkins and Kalant 1972; Isselbacher and Greenberger 1964; Lieber et al. 1963; Rubin and Lieber 1969) and were considered thoroughly in the *Third Special Report to the U.S. Congress on Alcohol and Health* (U.S. Department of Health, Education, and Welfare 1978). Therefore, these aspects of alcohol and the liver are not considered in this review. However, the relationship of moderate alcohol ingestion to HDL-C and suggestions for future directions in alcohol-liver-lipid research are discussed.

## ***Alcoholic Fatty Liver***

As mentioned above, among the most prominent effects of excess alcohol ingestion are metabolic derangements in the liver and peripheral tissues leading secondarily to excessive fat (triglyceride) accumulation in liver. The engorgement of liver cells with triglyceride droplets, and the associated cell injury, cause interference with many of the normal biochemical and metabolic functions of the liver cells. Clinically, patients with alcoholic fatty liver complain of nausea, vomiting, fever, loss of appetite, and weakness. On physical examination their skin and eyes appear yellow (jaundiced), their livers are enlarged, their abdomens may be swollen due to fluid accumulation, and biochemical tests of their liver functions are abnormal. The syndrome of alcoholic fatty liver is usually associated with some degree of hepatocellular injury leading to the term "alcoholic steatonecrosis" (Harinasuta and Zimmerman 1971). This condition is almost invariably a result of truly excessive alcohol consumption, frequently for several weeks.

Interest in the pathogenesis of alcoholic fatty liver has stimulated an enormous amount of research, but despite many years of intensive investigation there is still considerable debate about the relative importance of the many metabolic abnormalities that can lead to excessive triglyceride accumulation in the liver (Baraona and Lieber 1979; Hawkins and Kalant 1972; Lieber 1973). Research in this area has been stimulated by the clinical importance of alcoholic fatty liver as well as by the fascinating changes in adipose tissue and hepatic lipid metabolism that occur secondarily to alcohol metabolism.

A detailed review of the complex effects of ethanol on hepatic and adipose tissue lipid metabolism and their relationship to fatty liver is beyond the scope of this chapter. Because the many controversial issues concerning the pathogenesis of ethanol-induced fatty liver are still unresolved, an extensive discussion of an exhaustive literature would be required. Interested readers can refer to several recent articles for comprehensive reviews of the subject (Baraona and Lieber 1979; Hawkins and Kalant 1972; Isselbacher and Greenberger 1964).

## ***The Liver and Lipid Metabolism***

To explain the pathogenesis of ethanol-induced fatty liver, it is worthwhile first to discuss briefly certain aspects of hepatic lipid metabolism, the regulation of hepatic triglyceride secretion, and current concepts of fatty liver.

Normally, the liver contains only about 5 percent of its weight as fat. The triglycerides synthesized in the liver from fatty acid precursors are rapidly assembled into lipoproteins and secreted into the bloodstream. Fatty liver occurs when an imbalance between triglyceride synthesis and secretion leads to an accumulation of triglyceride droplets within

the cells and massive enlargement of individual hepatocytes. The hepatic synthesis of the triglyceride-carrying lipoproteins, called *very low density lipoproteins* (VLDL), is related directly to the availability of free fatty acids, which are transported in the blood bound to albumin. Free fatty acids are taken up by hepatocytes where they are used for triglyceride synthesis. The newly formed triglycerides are assembled with specific proteins (apoproteins) and other lipids to form VLDL molecules, which are secreted into the bloodstream (Morrisett et al. 1975).

The availability of fatty acids for hepatic triglyceride synthesis depends upon many factors, including type and quantity of diet, hormonal regulation (i.e., insulin availability, pituitary and adrenocortical hormones), and exogenous factors such as alcohol (Hawkins and Kalant 1972). Within the hepatocyte, the availability of free fatty acids for triglyceride synthesis depends on the status of complex biochemical regulatory mechanisms such as mitochondrial fatty acid oxidation, ketone body formation, endogenous fatty acid synthesis, and availability of precursors for glycerol synthesis. VLDL synthesis and secretion also depends on the availability of a specific apoprotein called *apoprotein B* (apoB); the assembly of apoB with triglyceride, phospholipid, and cholesterol; completion of the molecule by the addition of sugars to the apoproteins (glycosylation); and transport of the newly formed VLDL sequentially through several subcellular compartments prior to secretion (Eisenberg and Levy 1975).

Derangements in one or more of the metabolic regulatory steps leading to hepatic triglyceride synthesis, alterations in nutritional or hormonal status, or toxic influences on hepatocyte function thesis, assembly, intracellular transport, or secretion of VLDL. The net result of such changes is fatty liver.

### *Fatty Acid Metabolism*

To understand alcoholic fatty liver it is important to consider the physiology of fatty acid and triglyceride metabolism within the hepatocyte, since the pathogenesis of fatty liver is related intimately to derangements in the regulation of these metabolic processes (Newsholme 1976).

The fatty acids formed during breakdown (lipolysis) of blood triglycerides of dietary origin (chylomicrons) can be (1) utilized directly as a source of energy (i.e., in muscle); (2) taken up by adipose tissue cells where they are esterified again to triglycerides and stored; or (3) transported to the liver where they enter various biochemical pathways. The stored triglyceride in adipose tissue is an important source of energy that can be mobilized at time of need by once again undergoing lipolysis to release fatty acids into the bloodstream. The extent of triglyceride lipolysis in adipose tissue is under hormonal regulation. The release of fatty acids from adipose tissue provides a prime source of fatty acid influx into the liver under various changes in nutritional and



hormonal status (Renold and Cahill 1965). Within the hepatocyte the fatty acids may be (1) oxidized and used for energy, (2) converted to phospholipids, (3) used for the formation of cholesteryl esters, or (4) utilized for triglyceride synthesis. The release of triglyceride as newly synthesized VLDL provides another source of fatty acids. Like fatty acids of dietary origin, these fatty acids can be oxidized in muscle, stored as triglyceride in adipose tissue, or returned once again to the liver.

### *Biosynthesis and Secretion of Triglyceride-Rich Lipoproteins by the Liver*

The enzymes involved in triglyceride, cholesterol, and phospholipid synthesis are located in a subcellular compartment of the hepatocyte called the *smooth endoplasmic reticulum* (SER). Presumably, the newly formed lipids synthesized on the SER membranes are transported from the membranes into the tubular channels of the SER. Assembly of the lipid and proteins (apoproteins) to form VLDL probably occurs at the junction of the smooth and rough endoplasmic reticulum (RER). The final assembly, concentration, and glycosylation of the lipoproteins occur within another subcellular organelle called the *Golgi apparatus*. After final assembly of nascent VLDL in the Golgi, smooth-surfaced secretory vesicles derived from the Golgi and containing newly formed (nascent) VLDL migrate through the cytoplasm where they merge with the cell membrane of the hepatocyte and secrete the VLDL into the blood by a process called exocytosis (Stein et al. 1972).

There is still relatively little information available concerning the mechanism by which nascent lipoproteins in secretory vesicles are directed toward the cell membrane for secretion. Recent studies have demonstrated that colchicine and some related drugs can inhibit hepatic VLDL secretion (Stein and Stein 1973). The inhibitory effects of colchicine on VLDL secretion may be due to its interference with the formation of another class of subcellular organelles, the microtubules. Although microtubules probably have several functions, it has been postulated that they may direct the movement of secretory vesicles toward the cell membrane, thereby controlling the secretory process.

### *Triglyceride Metabolism in Adipose Cells*

Both exogenous and endogenous sources contribute free fatty acids for triglyceride synthesis by the liver, but the relative contribution from each source varies under different physiologic and hormonal conditions (Steinberg and Vaughan 1965). In the fasting state, the majority of free fatty acids utilized in hepatic triglyceride production are derived from the lipolysis of triglycerides in peripheral adipose tissue (Renold and Cahill 1965). This reaction, under the influence of a hormone-sensitive lipase, results in the liberation of free fatty acids and glycerol in the adipose cells. The uptake or release of free fatty acids by adipose tissue is regulated by neural and hormonal stimuli, and this process is enhanced

by the rich vascular supply of adipose tissue and its direct contiguity with nerve endings.

When caloric intake exceeds immediate metabolic needs after eating, triglyceride-rich fatty particles formed in the intestine (chylomicrons) supply free fatty acids to the liver. The amount of free fatty acids extracted by the liver is proportional to the concentration of free fatty acids in the portal vein, which carries blood from the intestine to the liver. Obviously, an increase in dietary triglyceride intake increases the quantity of fatty acids available for immediate energy needs and also provides a potential excess that is taken up by the liver or adipocytes. Free fatty acids entering the adipose tissue cells can be utilized directly for synthesizing triglycerides if glucose is available for synthesis of their glycerol portion.

### *Fatty Acid Mobilization*

Mobilization of fatty acids from adipose tissue is subject to numerous regulatory mechanisms that determine the rate at which free fatty acids enter the bloodstream. Of extreme importance is an enzyme in the adipose tissue called hormone-sensitive lipase, whose ability to break down stored fat is activated by hormonal, nutritional, chemical, or nervous factors thereby providing a means of increasing the plasma free fatty acid concentration to satisfy energy requirements in various tissues (Steinberg and Vaughan 1965). The adrenal hormones epinephrine, norepinephrine, and adrenocortical steroids; the pituitary hormones ACTH and TSH; the thyroid hormone thyroxine; and the pancreatic hormone glucagon all stimulate activation of a chemical mediator called cyclic AMP. Since cyclic AMP activates hormone-sensitive lipase, the hormonal activation of cyclic AMP provides a regulatory mechanism to promote triglyceride breakdown (lipolysis).

The increase in blood triglycerides that occurs after acute alcohol ingestion has been attributed to effects on adipose tissue resulting in fatty acid mobilization and enhanced fatty acid uptake by the liver, followed up by increased triglyceride synthesis and secretion. These effects may be mediated by stimulation of the sympathetic nervous system as a "stress" response to alcohol. The stimulation releases hormones from the adrenal gland (norepinephrine) to cause adipose tissue lipolysis, regulate carbohydrate metabolism in the liver, impair peripheral glucose uptake, and suppress the release of insulin by the pancreas.

If indeed the rate of hepatic triglyceride synthesis is proportional to the concentration of free fatty acids delivered in the portal venous blood, then lipid accumulation could occur if there were an imbalance between triglyceride availability and lipoprotein assembly and/or secretion.

### *Role of the Liver in Fatty Acid Uptake and Utilization*

Fatty acids liberated from adipose tissue are carried in the bloodstream bound to albumin. Approximately one-third of the circulating fatty acids are removed by the liver, a third by skeletal muscle, and the rest by other tissues (Quarfordt and Goodman 1967). Hepatic triglyceride formation or accumulation is greatly affected by the rate at which fatty acids are presented to the liver.

After uptake of exogenously (dietary) or endogenously derived fatty acids, hepatic triglyceride formation occurs rapidly. The esterification of fatty acids to make triglycerides is closely linked to hepatic oxidative phosphorylation and depends on a ready supply of alpha-glycerophosphate, the precursor of glycerol, which forms the backbone of the triglyceride molecule. Alpha-glycerophosphate is supplied almost exclusively from glucose. The availability of fatty acid coenzyme A derivatives also controls the extent of triglyceride synthesis. In addition to triglyceride synthesis, other fates exist for fatty acids in the hepatocyte (Baraona and Lieber 1979). During fasting, or when metabolic demands are great, fatty acids are oxidized to acetoacetate and other "ketone" bodies that may be used for energy. Since fatty acid oxidation is important in removing excess lipid from the liver, lipid accumulation within the organ does not occur ordinarily.

The rate of hepatic triglyceride synthesis is usually balanced by an approximately equal rate of hepatic secretion of triglyceride, but acute stresses of the system, as in extensive mobilization of fatty acid from adipose tissue or a rapid and prolonged increase in dietary chylomicron triglyceride, can result in increased hepatic triglyceride synthesis. Hepatic triglyceride formation or accumulation is greatly affected by the rate at which fatty acids are presented to the liver (Spitzer and McElroy 1960).

The liver may respond to an increased fatty acid influx by increasing the rate of triglyceride, lipoprotein, and ketone body synthesis, but the extent to which the activity of these pathways may increase is limited. If the rate at which fatty acids are brought to the liver exceeds the liver's ability to metabolize them or its ability to resecrete them into the circulation as lipoproteins, fat will be stored within the hepatocytes.

### ***Pathogenesis of Fatty Liver***

The numerous theories proposed for the pathogenesis of alcoholic and other types of fatty liver are based on derangements of hepatic triglyceride synthesis and secretion (Stein et al. 1972). These theories include not only abnormalities of physiological and biochemical regulation but also derangements in the steps by which the VLDL lipid and apoproteins are synthesized and assembled into nascent lipoprotein particles, transported sequentially through subcellular compartments, and finally secreted from the liver cells into the bloodstream.



Singly or in combination, derangements of these events can be involved in the pathogenesis of fatty liver (Lombardi 1966). Thus an increased supply of fatty acids leading to an imbalance between triglyceride synthesis and secretion could result from enhanced fatty acid mobilization from adipose tissue, increased hepatic fatty acid synthesis, or decreased fatty acid oxidation by mitochondria in the liver cells. The secretion of triglycerides might be impaired as a consequence of inhibited apoprotein synthesis or of inadequate apoprotein formation that might occur when an excess triglyceride load is available for assembly into lipoproteins. Defects in one or more of the steps involved in the assembly, intracellular transport, or secretion of VLDL can also lead to fatty liver (Sabesin, Hawkins, Kuiken, and Ragland 1977). These defects include inhibition of VLDL transport from the endoplasmic reticulum to the Golgi complex; impaired Golgi function preventing the final glycosylation of VLDL apoproteins; decreased secretory vesicle formation; and interference with the movement of secretory vesicles to the cell membrane, possibly secondary to microtubule dysfunction, resulting in impaired VLDL secretion.

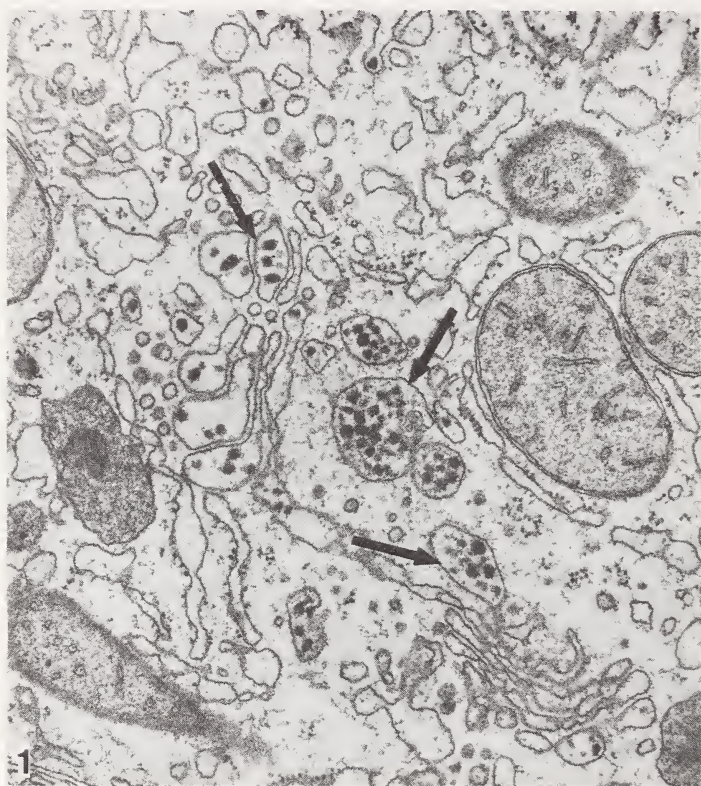
Although there are no definitive data concerning the relative importance of these mechanisms, some are undoubtedly more important than others, depending on the agent (drug, toxin) responsible for the production of fatty liver. The proposed mechanisms by which alcohol produces fatty liver are discussed below.

### ***Pathogenesis of Alcoholic Fatty Liver***

Administration of ethanol to rats rapidly enhances hepatic VLDL synthesis and secretion. This effect is illustrated in figure 1, which shows the marked proliferation of VLDL in rat hepatocyte Golgi and secretory vesicle formation 90 minutes after the intragastric administration of a very small amount of ethanol. These acute effects of ethanol appear to reflect enhanced mobilization of fatty acids from adipose tissue, perhaps secondary to the stress imposed by alcohol, and may also reflect increased hepatic fatty acid synthesis from acetate, a major metabolite of alcohol (Lieber and Rubin 1968a; Scheig 1970). Hepatic triglyceride formation is enhanced by the availability of excess fatty acids and by the increased production of alpha-glycerophosphate, also secondary to ethanol metabolism (Hawkins and Kalant 1972).

Alcohol ingestion, particularly if chronic and excessive, produces even more complex effects on peripheral and hepatic lipid metabolism and is also influenced by the availability of dietary lipids and the effects of alcohol on hepatocyte function (Lieber and DeCarli 1970; Lieber et al. 1965). The net result of such derangements is the development of fatty liver. A schematic representation of the various ways in which alcohol

Figure 1. Electron Microscopy of Rat Liver Obtained 90 Minutes After Intragastric Instillation of 1 ml 50 Percent w/v Ethanol



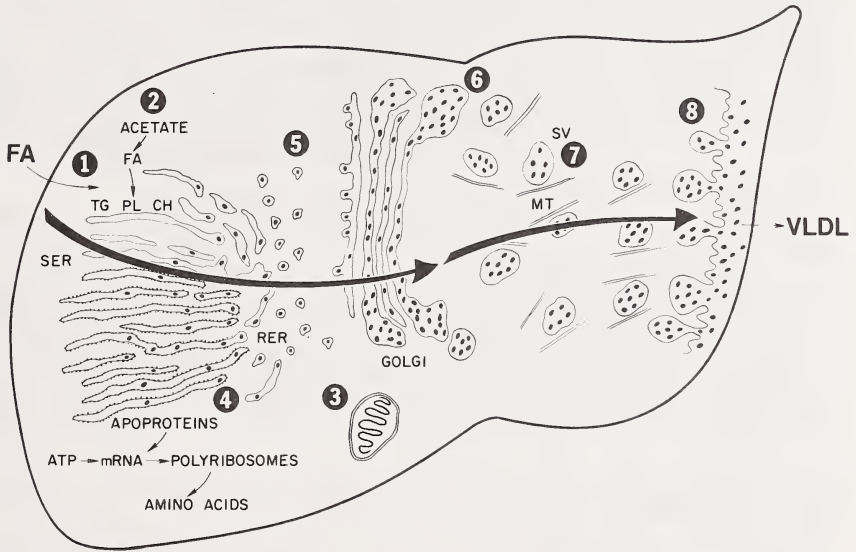
Note: Note the presence of numerous very low density lipoprotein particles in the hepatocyte Golgi zones (arrows). x23, 400

can cause fatty liver is illustrated in figure 2. The numbers in the diagram refer to postulated steps, discussed below, in the biosynthetic and secretory pathway leading to VLDL formation that can be deranged by alcohol.

Fatty liver can develop if there is an imbalance between the rate of triglyceride formation and the ability of the liver to assemble and/or secrete the triglycerides as VLDL. Factors that can affect this balance are as follows (refer to figure 2).

1. Ethanol may affect this process by increasing the supply of fatty acids to the liver, partly as a result of increased mobilization of fatty acids from adipose tissue. The mobilization may be the result of hormone-promoted triglyceride lipolysis in adipose tissue.

Figure 2. Schematic Representation of Pathogenesis of Ethanol-Induced Fatty Liver



Note: The numbers refer to possible sites of derangements in lipid metabolism and/or very low density lipoprotein formation and secretion. See text for details. FA, fatty acid; VLDL, very low density lipoprotein; TG, triglyceride; PL, phospholipid; CH, unesterified cholesterol; RER, rough endoplasmic reticulum; SV, secretory vesicle; MT, microtubule.

2. The supply of fatty acids is increased also by the formation of acetate, a product of ethanol metabolism.
3. If ethanol has caused hepatocyte injury, the mitochondrial oxidation of fatty acids may be impaired resulting in an excess of fatty acids which could then be used for triglyceride synthesis.



4. Ethanol-induced hepatocyte injury can also impair protein synthesis and thereby reduce the availability of apoproteins (apoB) for VLDL formation.

At the subcellular level it is possible that alcohol can affect one or more of the steps involved in the intracellular transport, packaging, and secretion of nascent VLDL (figure 2, steps 5-8). These include (5) the movement of vesicles containing nascent VLDL from the endoplasmic reticulum to the Golgi complex, (6) the glycosylation of nascent VLDL in the Golgi, and (6) the formation of secretory vesicles. The movement of secretory vesicles, containing nascent VLDL, to the cell membrane for secretion may be regulated by (7) microtubules. Ethanol has been shown to interfere with the export of several hepatic secretory proteins and there is some evidence that it interferes with microtubule formation (Baraona et al. 1977). Finally ethanol could inhibit (8) the exocytosis of VLDL again perhaps because of its effects on microtubules.

There is clinical and experimental evidence to support several of these mechanisms of producing fatty liver by ethanol excess. Let us now consider the experimental evidence upon which the current concepts are based. It should be emphasized that it is now well accepted that ethanol can directly injure the hepatocyte and that the development of fatty liver is not related to concomitant nutritional imbalances (Lieber and Rubin 1968*b*; Lieber et al. 1963; Rubin and Lieber 1968).

### *Effects of Ethanol on Hepatic Fatty Acid Synthesis*

Based on the metabolism of ethanol to acetate and the formation of excess NADH generated by ethanol oxidation it seems likely that ethanol could stimulate increased hepatic fatty acid synthesis. *In vitro* studies by Scheig (1971) showed incorporation of two-carbon fragments of ethanol into fatty acids and it was assumed that the excess NADH influenced the metabolism of acetyl-CoA to form fatty acids rather than being oxidized via the tricarboxylic acid cycle. However, *in vivo* studies have shown that ethanol does not enhance fatty acid synthesis. Instead, most of the ethanol is metabolized to acetaldehyde and thence to acetate, and it appears that the major influence of acetate and excess reducing equivalents (NADH) on fatty acid synthesis is the promotion of fatty acid chain elongation in the mitochondria (Lundquist et al. 1962; Savolainen et al. 1977).

### *Effect of Ethanol on Fatty Acid Esterification in the Liver*

Essential to triglyceride formation and thus to fatty liver is the esterification of fatty acids in hepatic cells. This process occurs in a subcellular compartment called the endoplasmic reticulum. The process is facilitated by ethanol metabolism since the increased ratio of NADH/NAD<sup>+</sup> which occurs as ethanol is oxidized to acetaldehyde enhances alpha-glycerophosphate formation from dihydroxyacetone-

phosphate (Nikkila and Ojala 1963). Since alpha-glycerophosphate is a substrate for triglyceride synthesis, this provides a mechanism for increased fat production (Ontko 1973).

Ethanol could also enhance fat formation in the liver by directing excess fatty acids from dietary or adipose tissue sources into triglyceride synthesis. Several *in vitro* studies have provided evidence of enhanced triglyceride synthesis from fatty acids under conditions of acute ethanol administration (Ontko 1973; Scheig and Isselbacher 1965). Enhanced triglyceride formation occurs only when ethanol is being metabolized and is related to stimulation of the microsomal enzymes involved in triglyceride synthesis (Joly et al. 1973; Mendenhall et al. 1969a). Whether similar effects occur during chronic ethanol administration is not known (Bustos et al. 1971).

### *Effects of Ethanol on Hepatic Fatty Acid Oxidation*

Another mechanism by which ethanol could stimulate triglyceride synthesis is by decreasing the oxidation of fatty acids in hepatocyte mitochondria, thereby increasing the pool of fatty acids available for triglyceride synthesis (Blomstrand and Kager 1973; Lieber and Schmid 1961; Mendenhall et al. 1969b). Some investigators favor this as the major mechanism of ethanol-induced fatty liver since there is experimental evidence that ethanol decreases fatty acid oxidation and produces structural and functional changes in the mitochondria of hepatocytes (Iseri et al. 1966; Rubin and Lieber 1967; Svoboda and Manning 1964).

Electron microscopic studies have shown ethanol-induced structural abnormalities in the mitochondria, including swelling, disruption of cristae, and unusual mitochondrial configurations (Rubin et al. 1970). Reduced activity of certain mitochondrial enzymes and decreased respiratory activity also have been demonstrated after ethanol administration (Rubin et al. 1970).

Furthermore, ethanol metabolism has certain effects that could directly influence fatty acid oxidation in mitochondria. These include utilization by the mitochondrial electron transport system of reducing equivalents derived from ethanol metabolism rather than two-carbon fragments from fatty acids, and possible depression of oxidation (Cederbaum et al. 1975; Gordon 1973; Rubin et al. 1972; Toth et al. 1973). These processes could cause an increase in fatty acid substrates for triglyceride synthesis and this could increase the fat content of the liver. This mechanism provides a very attractive explanation for increased triglyceride production, but its quantitative importance is not known. It is noteworthy that other substances such as glucose and sorbitol equally suppress hepatic fatty acid oxidation but do not cause fatty liver (Reboucas and Isselbacher 1961). More research in this important area is needed.

*Effects of Ethanol on Lipoprotein Synthesis and Secretion*

A major mechanism elucidated for the pathogenesis of many forms of experimental fatty liver is interference with the biosynthesis and/or secretion of lipoproteins (Lombardi 1966). In contrast to agents like ethionine or orotic acid which specifically inhibit VLDL secretion by the liver alcohol-induced fatty liver is associated with increased blood triglyceride levels rather than low triglycerides and VLDL (Jones et al. 1963). Although the data are conflicting regarding the exact effects of ethanol on hepatic VLDL formation and release, and are further confused by the diverse experimental conditions employed, it is likely that ethanol induces an imbalance between triglyceride formation and secretion (Mendenhall et al. 1969a; Schapiro et al. 1962; Seakins and Robinson 1964). Thus greatly enhanced triglyceride synthesis produced by ethanol could lead to fat accumulation if the assembly and export of VLDL do not keep up with the increased triglyceride load (Roheim et al. 1965). If this occurs then fatty liver as well as hypertriglyceridemia would ensue. Many patients with acute alcoholic fatty liver also have hyperlipidemia, but, as will be seen later, the hyperlipidemia is probably secondary to *increased* hepatic VLDL release and *decreased* blood triglyceride removal. In contrast, when fatty liver occurs in a "failing" liver it is not uncommon to find depressed blood triglycerides and cholesterol (Alexander et al. 1963).

*Effects of Ethanol on Fatty Acid Mobilization from Adipose Tissue*

There is still a major controversy regarding the importance of ethanol-induced free fatty acid mobilization from adipose tissue as a source of precursors for hepatic triglyceride formation (Baraona and Lieber 1979; Isselbacher and Greenberger 1964). There is no question that ethanol stimulates free fatty acid release from composition of the liver reflects the adipose tissue of origin (Schapiro et al. 1965). This could be a stress response mediated by norepinephrine since it can be inhibited by adrenalectomy or drugs that block the action of catecholamines (Bouchier and Dawson 1964).

The effect of ethanol on free fatty acid mobilization depends on the dose of ethanol, the acuteness or chronicity of its administration, and the presence or absence of dietary fat (Brodie et al. 1961; Kessler and Yalovsky-Mishkin 1966; Lieber et al. 1966; Mallov 1961; Poggi and DiLuzio 1964). There is also some evidence that acetate, a product of ethanol oxidation, can inhibit free fatty acid release from adipose tissue (Crouse et al. 1968). When dietary fat and alcohol are present together the hepatic lipids tend to reflect those in the dietary fat (Mendenhall 1972). The best explanation for all of these findings is that the source of the free fatty acids in the liver may vary with nutritional status and the amount and chronicity of alcohol ingestion. What is important for the development of fatty liver is the supply of free fatty acids since without an increase in fatty acids the hepatocyte is limited in its ability to synthesize triglycerides.



Many other hypotheses have been advanced to explain alcoholic fatty liver, and considerable research is still going on in an effort to understand the mechanisms involved. The effects of ethanol on mitochondrial membrane lipid peroxidation, interference with microtubule formation or function, and other aspects of the effects of ethanol on hepatocyte subcellular organelles are being investigated (Baraona et al. 1977; DiLuzio 1966; DiLuzio and Hartman 1969).

## ***Effects of Alcohol on Blood Lipids***

Hypertriglyceridemia associated with alcohol intake has been well documented in man for many years (Albrink and Klatzkin 1957; Chait et al. 1972; Zieve 1958). This effect occurs in the absence of ethanol-induced hepatic toxicity but, as will be seen later, is also a prominent feature of alcoholic fatty liver and alcoholic hepatitis.

The consensus of many studies, although certainly not unanimous, appears to be that alcohol causes hypertriglyceridemia in either the fasting state or when taken before eating. However, when alcohol is taken with a fatty meal the resulting hypertriglyceridemia is much greater (Barboriak and Meade 1968a; Brewster et al. 1966; Wilson et al. 1970). Furthermore, the elevation of triglycerides is related to the level of *fasting* plasma triglycerides; individuals who are usually hypertriglyceridemic have a greater elevation of triglycerides after alcohol than normals.

Hypertriglyceridemia induced by alcohol is more prolonged (clearance delayed) than the usual elevation of blood triglycerides that occurs after eating. There is some evidence that the delay in triglyceride removal from the blood is due to an impairment in triglyceride lipolysis, but this has not been proven (Jones et al. 1963). Alcohol seems to act primarily by increasing the synthesis and secretion of triglycerides as very low density lipoproteins (VLDL) by the liver, although there may also be an intestinal component, especially when alcohol is taken with a fatty meal.

Both orally and intravenously administered alcohol over an 8-hour period were found to cause a 100 percent increase in plasma triglycerides associated with a 60 to 80 percent decrease in plasma free fatty acids (Jones et al. 1963). That the rise in plasma triglycerides was due primarily to incorporation of plasma free fatty acids into triglycerides by the liver was confirmed by studies involving the infusion of a radioactive fatty acid (palmitate), which was incorporated within 1 hour into VLDL (Nestel and Hirsch 1965). These findings were confirmed in the rat, and it was also found that the fatty acids synthesized by the liver were not the source of the hypertriglyceridemia following alcohol administration (Bezman-Tarcher et al. 1966). Other studies have shown that drinking before meals caused significantly high postprandial plasma triglyceride levels and that the effect was not due to decreased

triglyceride removal from blood but rather to increased hepatic triglyceride synthesis and release (Brewster et al. 1966).

In a careful study of the effect of alcohol on fasting blood triglyceride levels and triglyceride levels following ingestion of corn oil, it was found that triglyceride clearance was delayed by alcohol following the fat load and that alcohol produced an increase in triglycerides in both the fasting and fed state (Verdy and Gattereau 1967). However, the availability of the lipases required to break down the blood triglycerides was not affected by alcohol (Verdy and Gattereau 1967). An investigation in man of triglyceride absorption and clearance with and without alcohol suggested that the hyperlipemia induced by preprandial alcohol and a fat meal might represent a delay in clearing the absorbed fat (Barboriak and Meade 1968b).

The effect of ethanol on plasma triglycerides during fasting and after a fatty meal was investigated in normolipidemic and hyperlipidemic subjects (Wilson et al. 1970). Fat and ethanol caused a prolonged and augmented rise in plasma triglycerides that was aggravated by preexisting hyperlipemia. Fat alone led to a rise of shorter duration. Alcohol had no effect on lipolytic activity, and most of the prolonged rise in triglycerides was due to VLDL, whereas chylomicrons (fat particles formed by the intestine) rose and fell more rapidly. Furthermore, the fatty acid composition of the VLDL reflected that of the ingested fat, suggesting that the VLDL were formed by reincorporation of dietary fatty acids into triglycerides by the liver.

The effects of ethanol on intestinal VLDL production were studied by infusing alcohol into the small intestine in the absence of fat (Mistilis and Ockner 1972). Ethanol increased the production of VLDL by the intestine, suggesting that the intestine used plasma free fatty acids as a source for triglyceride synthesis. The importance of hepatic triglyceride production after ethanol was shown by studies demonstrating that the ethanol-induced hypertriglyceridemia in rats is blocked by feeding orotic acid, which interferes with hepatic secretion of triglycerides as VLDL (Hernell and Johnson 1973). Ethanol increases the postprandial triglyceride response in both normolipidemic and hyperlipidemic individuals, but increases triglycerides in the fasting state only in subjects with hyperlipidemia (Ginsberg et al. 1974). These observations are interesting in view of the observation that feeding rats enhances their hyperlipidemic response to acute alcohol administration (Morland and Oye 1974).

The results of a study in which radioactively labeled chylomicrons were infused into rats that were fed alcohol chronically revealed only slight impairment of chylomicron-triglyceride clearance but significant delay in chylomicron-cholesterol clearance. This suggests an accumulation of chylomicron remnants (Redgrave and Martin 1977). Nocturnal and morning hypertriglyceridemia and hyperinsulinemia have been demonstrated following administration of moderate amounts of alcohol in the evening. Hyperlipidemics demonstrated a more sustained hyper-

insulinemia compared to normolipidemics. The increase in triglycerides was highly correlated with the increase in insulin.

The consensus of the above studies, although certainly not unanimous, appears to be that alcohol induces hypertriglyceridemia in either the fasting state or when taken preprandially. Alcohol taken with a fatty meal causes much more triglyceridemia. The response is directly related to the level of fasting plasma triglycerides; i.e., hyperlipidemics show a greater response than normolipidemics. Hypertriglyceridemia induced by alcohol is more prolonged (clearance delayed) as compared to normal postprandial hyperlipemia. Lipoprotein lipase deficiency does not seem to be a factor in the alcohol response. Alcohol appears to act primarily by increasing synthesis and secretion of VLDL by the liver, although there may also be an intestinal component, particularly when alcohol is taken with a fatty meal.

It is evident from the above discussion of the complexities of lipoprotein and ethanol metabolism and the secondary effects imposed by liver injury that the pathogenesis of ethanol-induced hyperlipidemia is multifactorial. These complexities are shown schematically in figure 3, with the various steps leading to hyperlipidemia numbered. Let us now summarize briefly each of the possible steps whereby ethanol can lead to hyperlipidemia, referring to the numbers in figure 3. (Evidence for and against the importance of several of these steps has been discussed above. Ethanol may directly increase intestinal VLDL formation even in the absence of dietary fat but this probably contributes little to hypertriglyceridemia.)

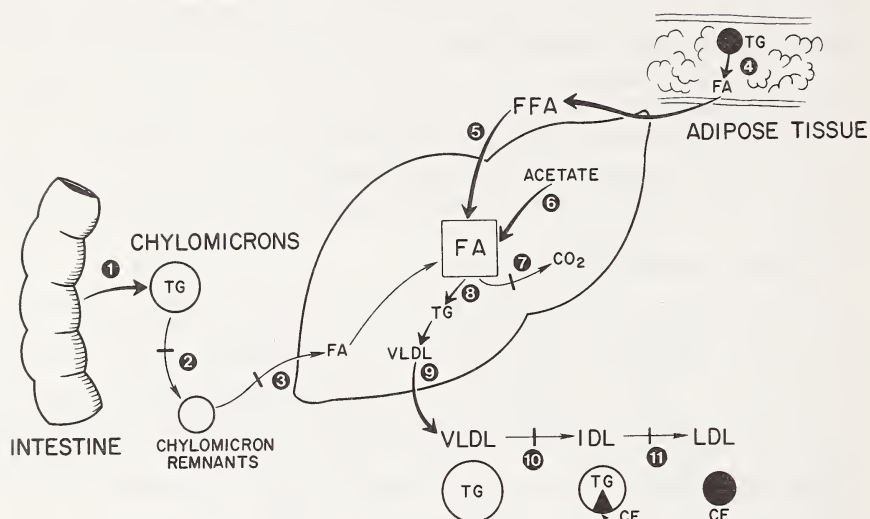
Dietary fat (1) can be important since (2) the chylomicrons may be metabolized slowly because of inadequate lipolysis (i.e., deficiency of lipoprotein lipase or lack of the specific protein—apoprotein C-II—which activates the lipase reaction) or (3) chylomicron remnants once formed may be removed slowly by the liver perhaps because of hepatocyte injury or decreased hepatic triglyceride lipase activity.

As mentioned previously, alcohol encourages hepatic triglyceride formation by (4) enhancing triglyceride lipolysis in adipose tissue, releasing free fatty acids which are then (5) taken up by the liver and contribute to an increased hepatic pool of fatty acids for triglyceride synthesis. This pool of fatty acids is increased also by fatty acid synthesis from (6) acetate and (7) decreased mitochondrial fatty acid oxidation. Triglyceride synthesis is greatly enhanced by the increased availability of (8) fatty acids and alpha-glycerophosphate.

The newly formed triglycerides are then incorporated into (9) VLDL and are secreted into the blood, where they increase the concentration of plasma triglycerides. Once in the blood, VLDL triglycerides are ordinarily removed rapidly by the lipolytic activity of lipoprotein lipase, which results in the formation of intermediate density lipoprotein (IDL) and low density lipoprotein (LDL). However, impaired (10) VLDL and (11) IDL catabolism in alcoholics with liver injury may lead to hypertri-



Figure 3. Schematic Representation of Pathogenesis of Alcoholic Hyperlipidemia



Note: Numbers refer to possible sites of deranged lipid and/or lipoprotein metabolism. See text for details. FA, fatty acids; FFA, free fatty acids; TG, triglyceride; CE, cholesteryl ester; VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; LDL, low density lipoprotein.

glyceridemia. These catabolic defects, which are discussed thoroughly in a later section, reflect lipolytic abnormalities and impaired cholesterol esterification. Although the acute hypertriglyceridemia is ordinarily benign, occasionally massive hypertriglyceridemia results in severe pancreatitis. The importance of chronic hypertriglyceridemia as a risk factor for atherosclerotic vascular disease also must be considered.

## ***Role of the Liver in Lipoprotein Metabolism***

The changes in blood lipids and lipoproteins that are associated with alcohol-induced hepatic injury are very intimately related to abnormalities in the biosynthesis and metabolism of lipids and lipoproteins. Since the liver is the central organ in many aspects of lipoprotein metabolism it is likely that the striking derangements in the concentration and composition of lipoproteins in patients with alcoholic hepatitis reflect an impairment of one or more of the lipoprotein biosynthetic or metabolic processes with which the liver is involved. In order to appreciate the importance of the liver in this regard, and the profound abnormalities which occur in alcoholic hepatitis, it is valuable to discuss briefly certain fundamental aspects of lipoprotein metabolism (Eisenberg and Levy 1975; Morrisett et al. 1975).

The main function of lipoproteins is the transport of lipids in the blood. Except for the intestinal secretion of fat droplets (chylomicrons) after a fat-containing meal, the liver is the major source of plasma lipoproteins. In addition to its role in lipoprotein formation, the liver has many other essential functions in lipoprotein metabolism (Sabesin 1979; Sabesin et al. 1979, 1980): in addition to forming and secreting very low density lipoproteins (VLDL), the liver secretes high density lipoproteins (HDL), and is the synthetic site of several key enzymes and proteins (apoproteins) that regulate lipoprotein metabolism in the plasma and peripheral tissues. The liver also removes the end-products ("remnants") of plasma lipoprotein catabolism from the blood and degrades the remnant lipoproteins. The liver also helps to regulate total body cholesterol stores by secreting cholesterol into the bile.

### ***Characteristics of Plasma Lipoproteins***

The major classes of plasma lipids, triglycerides, cholesterol, cholesteryl esters, and phospholipids, combine in varying proportions with specific proteins (apoproteins) to form lipoprotein molecules, whose primary function is the transport of lipids in the watery environment of the blood. The structure of the lipoprotein molecule permits certain lipids (triglycerides, cholesteryl esters) which cannot ordinarily mix with water to form the core of a particle that is covered with a surface layer of cholesterol, phospholipids, and apoproteins.

Lipoprotein formation occurs primarily in hepatocytes (VLDL and HDL) and also within intestinal mucosal epithelial cells in response to dietary lipid absorption (chylomicrons). The lipoproteins are then secreted into the plasma or lymph where they undergo rapid metabolic transformations involving triglyceride removal, cholesterol esterification, and exchanges of lipids and apoproteins. By this process lipoproteins are formed which are similar in size and composition to the lipoprotein particles that can be isolated from the blood by ultracentrifugation.

Certain apoproteins, in addition to solubilizing the various lipid classes, also serve other important functions in lipoprotein metabolism

(Schaefer et al. 1978). Thus, apoC-II and apoA-I are cofactors for lipoprotein lipase (LPL) and lecithin:cholesterol acyltransferase (LCAT), respectively. These are key plasma enzymes essential for the lipolysis of triglyceride-rich lipoproteins (chylomicrons and VLDL) and for cholesterol esterification. Apoprotein B in low density lipoproteins (LDL) binds specifically to cell receptors allowing uptake and intracellular metabolism of cholesteryl esters, in this manner regulating plasma and intracellular cholesterol concentration (Goldstein and Brown 1977).

Lipoproteins can be segregated into four major classes on the basis of their hydrated density (as determined by flotation in the ultracentrifuge), size, electrophoretic mobility, or biosynthetic site of origin. Triglyceride-rich lipoproteins that have a density (relative to water) of less than 0.95, do not migrate on electrophoresis, and are primarily of intestinal origin are called chylomicrons. Triglyceride-rich lipoproteins of density 0.95-1.006, which exhibit pre-beta electrophoretic mobility and are primarily of hepatic origin, are designated VLDL. Lipoproteins isolated at a density of 1.006-1.063 are called low density lipoproteins (LDL). LDL have beta electrophoretic mobility, are rich in cholesteryl esters, and are formed exclusively in plasma as products of VLDL catabolism (Schaefer et al. 1978). The remaining major class, the HDL, are isolated at a density of 1.063-1.216, are rich in protein and phospholipids, and have alpha electrophoretic mobility.

Just as there is a great deal of diversity in lipid content within the lipoprotein density classes, there is even further heterogeneity in their apoprotein composition. Individual apoproteins are designated by the prefix "apo" followed by a letter designation for type. In addition to their structural importance in the lipoprotein molecule, each of the apoproteins may have a specific function in some aspect of lipoprotein metabolism. When isolated by ultracentrifugation and then stained, the lipoproteins in each density class can be visualized directly in the electron microscope, where they appear as rather homogeneous spherical particles.

### *Lipoprotein Lipase (LPL)*

The major enzyme involved in the metabolism of triglyceride-rich plasma lipoproteins is LPL, which hydrolyzes (removes) the triglycerides of chylomicrons and VLDL. The liver is important for LPL activity since it synthesizes and secretes apoC-II, a required activator for LPL (30). During metabolism, chylomicrons become depleted of triglycerides and enriched in cholesteryl esters. These particles, now called chylomicron remnants, are cleared by the liver as intact particles, presumably by a receptor-mediated process (Floren and Nilsson 1977; Redgrave 1970).

### *Lecithin: Cholesterol Acyltransferase (LCAT)*

It is evident that LCAT is derived from the liver since it is essentially absent in hepatectomized animals (34) and LCAT deficiency occurs in



many types of human and experimental liver injury (Sabesin, Hawkins, Kuiken, and Ragland 1977; Sabesin et al. 1975; Sabesin, Kuiken, and Ragland 1978). The basic function of LCAT is the transfer of a fatty acyl group, usually polyunsaturated, from lecithin, a phospholipid, to unesterified cholesterol to form cholesteryl esters. LCAT is responsible for the formation of nearly all the cholesteryl esters in the blood and uses the newly formed (nascent) HDL from the liver and intestine as its principal substrate. As a result of LCAT's action, nascent HDL is converted to normal HDL, which is rich in cholesteryl ester (Tall and Small 1978).

### *Hepatic Triglyceride Lipase*

The mechanism by which chylomicron remnants are removed by the liver and the remaining triglyceride in the remnants hydrolyzed is uncertain. A lipolytic enzyme of liver called hepatic triglyceride lipase, with activity against mono-, di-, and triglycerides, has been postulated to have a role in both processes (LaRosa et al. 1972).

### *High Density Lipoprotein Uptake*

Certain cells in the liver, the Kupffer cells, possess a high capacity to degrade HDL and account for more than 50 percent of the liver's capacity for HDL protein breakdown and cholesteryl ester hydrolysis (VanBerkel et al. 1977). Binding of HDL to hepatocytes may be related to a hepatocyte membrane receptor, and liver lysosomes may be the principal site of HDL proteolytic degradation, just as they appear to be for chylomicron remnants.

### *Overview of the Liver and Lipoprotein Metabolism*

Plasma lipoproteins are constantly being synthesized and degraded. Their metabolism is dependent on complex enzymatic reactions and on transfer and exchange of lipids and apoproteins between each class of particles. Figure 4 is a simplified scheme depicting the major aspects of plasma lipoprotein metabolism. During this process, nascent particles acquire new apoproteins, cholesteryl esters are synthesized, and triglycerides are hydrolyzed; thus lipoproteins of drastically different composition and structure are formed. After chylomicrons enter the lymph they acquire the apoC peptides, perhaps by transfer from HDL. The acquisition of apoC-II initiates lipolysis (removal) of the triglyceride core of chylomicrons. Concomitant with triglyceride lipolysis there is loss of phospholipid, some unesterified cholesterol, apoA-I, and apoC from the chylomicron surface. These lipid and apoprotein losses leave a chylomicron remnant containing apoB, cholesteryl esters, and some residual triglyceride, which are then cleared by the liver. The triglycerides in VLDL are also hydrolyzed by LPL, and similar transfers of surface lipids and apoproteins occur as described for chylomicrons. VLDL is converted into intermediate density particles (IDL), then into LDL, as additional triglyceride is hydrolyzed and phospholipid, apoA-I,

apoA-II, and apoC peptides are removed. The smaller particle that results contains mostly cholesteryl esters and apoB, the constituents of LDL.

When HDL are secreted by the liver or intestine (nascent HDL), they contain mostly unesterified cholesterol and appear by electron microscopy as bilamellar discs instead of the spherical particles isolated from the blood (Hamilton et al. 1976). Nascent HDL is the substrate for LCAT and is converted from discoidal to spherical particles as the newly formed apolar cholesteryl esters form the particle core and are covered on the surface by apoproteins, unesterified cholesterol, and phospholipid. The cholesteryl esters then are transferred to the VLDL→IDL→LDL pathway perhaps with apoE and apoC. Thus, nascent VLDL become enriched with apoC and apoE and in turn, during catabolism, provide a pool of unesterified cholesterol, phospholipid, and apoC used to replenish HDL. HDL may transport unesterified cholesterol from peripheral cells, thus preventing an excessive accumulation of cellular cholesterol and providing a source of cholesterol for subsequent esterification. The LDL are a primary source of cholesterol for extrahepatic cells. Binding of LDL to cells is mediated by specific receptors. After uptake, the cholesteryl esters of LDL are hydrolyzed by a cholesteryl esterase forming free cholesterol, a process that regulates cell cholesterol content.

### ***Deranged Plasma Lipoprotein Metabolism Secondary to Ethanol-Induced Liver Injury***

It is important to emphasize that ethanol produces changes in the concentration of blood lipids and lipoproteins that reflect the presence or absence of alcoholic liver injury. These changes represent a progression from acute effects of alcohol on adipose tissue and hepatic lipid metabolism, to abnormalities associated with hepatocellular injury, and finally to profound secondary effects on lipid and lipoprotein metabolism that accompany very severe hepatic disease (Baraona and Lieber 1979). Thus the lipid and lipoprotein changes in alcoholic hepatitis patients are quite different from those that occur in normal subjects after acute alcohol administration, or from those found in fasting blood samples from moderate drinkers or even chronic alcoholics without evidence of liver disease.

The changes in the composition and concentration of plasma lipids and lipoproteins that are very commonly associated with alcoholic liver disease can be explained, in part, by specific abnormalities in lipoprotein synthesis and metabolism that are secondary to hepatocellular injury and deranged lipid metabolism produced by ethanol (Sabesin et al. 1980).





and fat accumulation (Galambos 1972; Harinasuta and Zimmerman 1971). Invariably patients with alcoholic hepatitis have indulged in massive ethanol consumption for several weeks before the clinical manifestations of jaundice, weakness, fever, and abdominal pain become manifest. The specific diagnosis is based on histopathological findings of hepatocyte necrosis, the presence of so-called "alcoholic hyaline" in the cytoplasm, inflammatory exudates of lymphocytes and polymorphonuclear leukocytes, and enlargement of individual hepatocytes by an accumulation of triglyceride droplets.

The plasma lipids in 15 patients with acute alcoholic hepatitis and during recovery are shown in table 1. A characteristic feature of acute alcoholic hepatitis is hypertriglyceridemia. Although the triglycerides are usually modestly elevated in most patients (range in this study, 99-475 mg/dl), occasionally massive hypertriglyceridemia occurs. The hypertriglyceridemia is often accompanied by increases in total plasma cholesterol, but the most striking abnormality found consistently in alcoholic hepatitis is the profound decrease in the percentage of cholesteryl esters (table 1). In this group of patients the mean level of cholesteryl esters in plasma was only 12 percent, in contrast to normal values of 70 to 75 percent. In some patients with very severe disease, no cholesteryl esters were present in the blood.

Table 1. Blood Lipids in Alcoholic Hepatitis

	Acute			Convalescent		
	TG (mg/dl)	CH (mg/dl)	CE (Percent)	TG (mg/dl)	CH (mg/dl)	CE (Percent)
Mean (N=15)	263	200	12	158	232	51
Range	99-475	34-447	0-39	63-310	41-227	11-72

Note: TG, triglycerides; CH, total plasma cholesterol; CE, percent cholesteryl esters. Normal values: TG 50-150 mg/dl; CH 150-225 mg/dl; CE 70-75 percent.

The defect in cholesterol esterification reflects deficiency of the enzyme LCAT. As will be discussed later, the inability to form cholesteryl esters is a key factor in the many other abnormalities of lipoprotein composition and metabolism that occur in alcoholic hepatitis. With hospitalization and abstinence from alcohol, the plasma lipids gradually normalize, reflecting the restoration of normal hepatic function and increased LCAT activity (Sabesin, Hawkins, Bertram, Mann, and Peace 1978). In some patients with severe alcoholic hepatitis, plasma lipids may be decreased. A low and decreasing concentration of triglycerides and cholesterol in blood is an ominous reflection of impaired biosynthetic function in liver cells and is often associated with intractable hepatic failure or a very prolonged convalescence. In these patients the liver is usually greatly enlarged by massive fat accumulation.

*Plasma Lipoprotein Electrophoretic Abnormalities in Alcoholic Hepatitis*

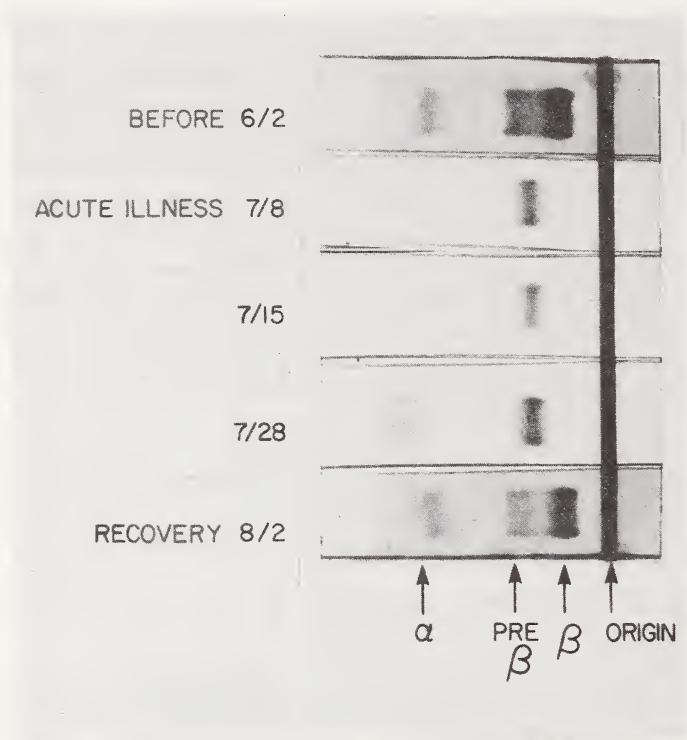
Patients with alcoholic hepatitis have lipoprotein electrophoretic abnormalities at the onset of illness which gradually normalize with the improvement of hepatic function (figure 5). The characteristic lipoprotein electrophoretic abnormality is a greatly reduced or absent alpha (HDL) band, absent pre-beta (VLDL), and the appearance of a single broad densely staining band with mobility between beta (LDL) and pre-beta (figure 5). The normal identity of alpha, beta, and pre-beta bands with HDL, LDL, and VLDL does not hold true in alcoholic liver disease (Sabesin, Frase, and Ragland 1977; Thallasinos et al. 1975). Patients with acute alcoholic hepatitis with an absent alpha band on electrophoresis have HDL of abnormal composition and morphology, which can be isolated from the blood, and VLDL can be isolated by ultracentrifugation even though pre-beta lipoproteins are absent on electrophoresis (Seidel et al. 1972). The abnormal HDL of liver disease seems to represent a nascent HDL that cannot be converted to 'normal' HDL because of the deficiency of LCAT secondary to liver cell injury (Ragland, Bertram, and Sabesin 1978).

*Disturbances of Cholesterol Esterification and LCAT Deficiency in Alcoholic Hepatitis*

Impaired cholesterol esterification is characteristic of alcoholic hepatitis. The quantity of cholesteryl esters correlates directly with the plasma LCAT activity. Plasma LCAT activity is sufficient to account for all the esterified cholesterol in plasma. The importance of the liver in the production of this key enzyme, as well as its cofactor (apoprotein A-I) and principal substrate (unesterified cholesterol), provides a sufficient basis to explain the disturbances of cholesterol esterification that accompany alcoholic and other types of liver injury characterized by acute hepatocellular necrosis. Plasma from patients with liver disease contains increased lecithin and unesterified cholesterol and decreased lysolecithin and cholesteryl esters. These findings are strikingly similar to those found in patients with hereditary LCAT deficiency (Glomset et al. 1973). Familial LCAT deficiency is characterized by profound deficiency of cholesteryl esters in the *absence* of liver disease, confirming the negligible role of intrahepatic cholesteryl ester synthesis (Norum and Gjone 1967).

Patients with alcoholic hepatitis consistently have LCAT deficiency, and its degree generally parallels the extent of liver injury as assessed by clinical and laboratory criteria (Sabesin, Hawkins, Kuiken, and Ragland 1977; Sabesin, Hawkins, Bertram, Mann, and Peace 1978). The prognostic significance of the degree of LCAT deficiency has been emphasized, since patients with low activity seem to have a greater impairment of hepatic function and therefore a substantially poorer

Figure 5. Electrophoretic Patterns in Alcoholic Liver Disease



Note: Plasma agarose electrophoretic patterns obtained during the course of illness and recovery in a patient with alcoholic fatty liver and alcoholic hepatitis.

prognosis than patients with lesser degrees of impaired LCAT activity. Increasing LCAT and plasma cholesteryl esters occur with clinical recovery, an observation that strongly suggests a causal relationship. It is likely that the LCAT deficiency arises from decreased enzyme synthesis and/or release by the damaged liver.

#### *Lipoprotein Compositional and Ultrastructural Abnormalities in Alcoholic Hepatitis*

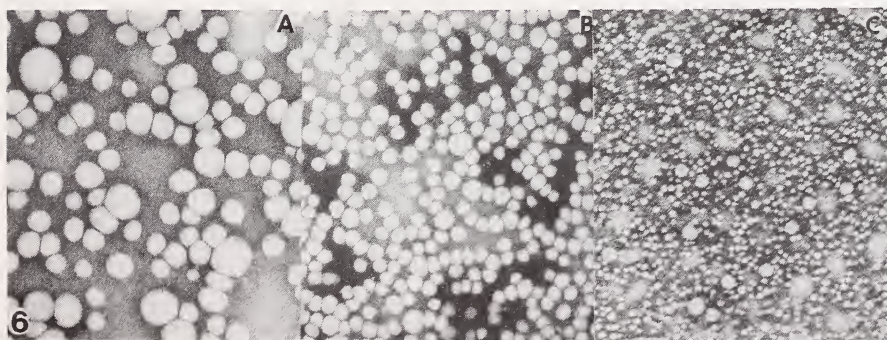
Detailed compositional studies of lipoprotein fractions isolated by ultracentrifugation, performed at various intervals throughout the course of illness in patients with alcoholic hepatitis, reveal compositional abnormalities in each of the fractions (Sabesin, Hawkins, Kuiken, and Ragland 1977). Most prominent are profound depressions in the percentage of cholesteryl esters, which can remain extremely low for many weeks before they gradually begin to return to normal. In VLDL,



the decrease in cholesteryl esters is accompanied by a moderate increase in phospholipids. In addition to a striking decrease in the percent cholesteryl esters in LDL, this fraction is characterized by a fourfold increase in triglycerides and an enrichment in phospholipids. The HDL fraction is remarkable for the decrease in the percentage of cholesteryl esters, which can persist at very low levels for several months in very sick patients.

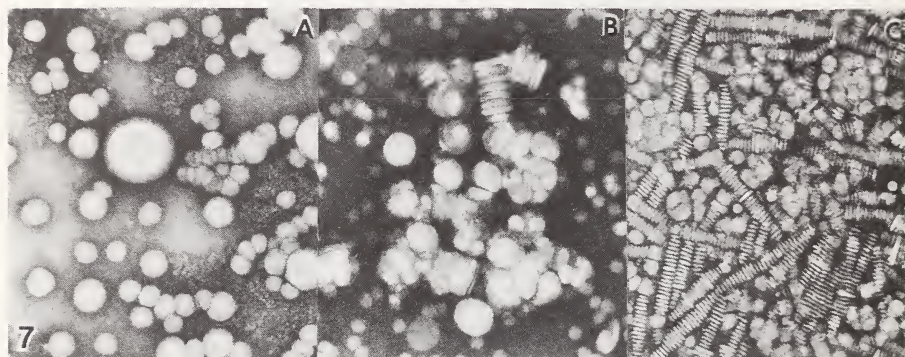
Compositional abnormalities of the lipoproteins are associated with ultrastructural alterations that can be observed by electron microscopy of negatively stained lipoproteins isolated from plasma by sequential ultracentrifugation. In normal plasma (figure 6), lipoproteins appear as uniform spherical structures of gradually decreasing size: VLDL, 300 to 750 Å (Å = angstroms); LDL, 170 to 260 Å; and HDL, 90 to 120 Å. The ultrastructure of lipoproteins isolated from the plasma of a patient with alcoholic hepatitis a few days after admission to the hospital is illustrated in figure 7. The VLDL fraction contained particles similar in structure and size to normal VLDL. The LDL, isolated at  $1.006 < d < 1.063$ , contained some spherical particles similar in appearance and size to normal LDL (mean diameter 225 Å), although many particles were much larger (500 Å). In some preparations the lipoproteins

Figure 6. Electron Microscopic Appearance of Normal Human Plasma Lipoproteins Negatively Stained With Phosphotungstic Acid



Note: A, very low density lipoproteins; B, low density lipoproteins; C, high density lipoproteins. Magnifications,  $\times 100,000$ .

Figure 7. Electron Microscopic Appearance of Plasma Lipoproteins Negatively Stained With Phosphotungstic Acid Obtained From a Patient With Alcoholic Hepatitis



Note: See text for explanation of ultrastructure abnormalities. A, very low density lipoproteins; B, low density lipoproteins; C, high density lipoproteins. Magnifications,  $\times 100,000$ .

appeared predominantly as bilamellar vesicles and discs measuring 450-500 Å in diameter and 105-130 Å in thickness (figure 7B). The HDL fractions contained some spherical particles of approximately normal HDL size, but most of the lipoproteins appeared as long chains of stacked bilamellar discs measuring 150-240 Å in diameter and 30-50 Å in thickness (figure 7C).

Compositional analysis of cholesterol and apoA-I, the major apoprotein of HDL, reveal abnormalities in whole plasma and in lipoprotein fractions in patients with typical alcoholic hepatitis. Thus in a typical patient at the beginning of illness, apoA-I was almost absent in whole plasma (5.0 mg/dl, normal: 120 mg/dl). The HDL fraction was also apoA-I deficient (5.0 mg/dl, normal: 105 mg/dl). The cholesterol content of the HDL was reduced to 3.0 mg/dl (normal: 62 mg/dl).

### *Apoprotein Composition in Alcoholic Hepatitis*

An analysis of the specific apoprotein composition and concentration in the VLDL, LDL, and HDL of patients with alcoholic hepatitis reveals remarkable abnormalities that can probably be attributed to defective lipoprotein metabolism (Ragland, Heppner, and Sabesin 1978). Characteristically, the VLDL are enriched in apoB, but the C peptides and apoE may be nearly absent. The LDL fraction contains apoB essentially similar to that in normal LDL, but the apoprotein content of HDL is strikingly abnormal. Normal HDL contain apoA-I, apoA-II, the apoC peptides, and a trace of apoE. In contrast the predominant apoprotein in alcoholic hepatitis HDL is apoE, and apoA-I is severely deficient.

With recovery from alcoholic hepatitis the apoprotein composition of the VLDL and HDL gradually returns to normal. This is associated with an increase in plasma LCAT activity and a corresponding increase in the percentage of cholesteryl esters in plasma. The return toward normal of the apoproteins in the isolated lipoprotein fractions is characterized by a decrease in apoE in HDL and an increase in apoA-I. The relative proportion of apoB in VLDL gradually decreases while apoC and apoE content increases.

### *Overview of Lipoprotein Metabolism in Alcoholic Hepatitis*

It is evident that alcoholic hepatitis is associated with many abnormalities in the concentration and composition of blood lipids and lipoproteins. The cause of these changes is multifactorial, reflecting complex biosynthetic, enzymatic, and catabolic derangements in lipoprotein catabolism. Most important are the effects of alcohol on lipid metabolism and the deleterious effects of alcohol on hepatocellular function. These result in excessive hepatic secretion of triglyceride-rich VLDL, but because of associated apoprotein biosynthetic defects, LCAT deficiency, and possibly defects in triglyceride lipolysis, remnant removal, and/or hepatocyte triglyceride lipase deficiency, striking derangements in lipoprotein metabolism occur (Freeman et al. 1977; Sabesin et al. 1979, 1980).



An interpretation of the compositional abnormalities in alcoholic hepatitis is compatible with the hypothesis that the liver secretes primarily two lipoprotein types: nascent HDL, whose major apoprotein is apoE; and nascent VLDL, containing only apoB. Normally nascent HDL is acted upon by LCAT, and the cholesteryl esters formed are transferred to the nascent VLDL→LDL pathway along with apoE and apoC. As a result, HDL containing primarily apoA-I is the major component of the HDL fraction. In alcoholic hepatitis, in which there may be almost complete absence of LCAT in plasma, nascent HDL is not metabolized and accumulates in plasma. As a result, cholesteryl esters are not formed and thus not transferred to the VLDL→LDL pathway along with apoE and apoC. Thus nascent VLDL with an essentially normal lipid composition but containing primarily apoB accumulates. Partial hydrolysis of the triglyceride in nascent VLDL results in the accumulation of a triglyceride-rich fraction floating in the LDL density range (1.006-1.063). The lipoprotein fraction contains primarily apoB but its further metabolism to IDL and LDL is impaired, perhaps because of cholesterol ester deficiency and possibly also because of deficiency or absence of apoE and apoC.

### ***Relationship of Moderate Alcohol Ingestion to High Density Lipoprotein-Cholesterol Concentration***

In the past few years there has been enormous interest in the possibility that the levels of cholesterol contained in the blood HDL fraction (HDL-C) may be important in the pathogenesis of atherosclerosis (Castelli et al. 1977; Gordon et al. 1977; Miller and Miller 1975). Numerous epidemiological studies have provided statistical evidence of the protective effects of high concentrations of HDL-C, whereas low levels of HDL-C were positively correlated with coronary heart disease (CHD). These observations have stimulated a veritable flood of clinical and basic investigations related to HDL-C, HDL metabolism, and CHD. Factors that might elevate HDL-C have been sought. Among the latter are vigorous physical exercise, lean body mass, and, surprisingly, the ingestion of *moderate* amounts of alcohol (Ginsberg et al. 1974; Yano et al. 1977).

Although the mechanism of the protective effect of HDL-C is not known, it appears that the concentration of cholesterol in HDL is partly derived from cell membranes. Thus HDL might interact with cell membranes and serve as a "sink" for excess cholesterol. Adequate removal of cholesterol from cell membranes would prevent intracellular cholesterol accumulation and therefore presumably atherosclerosis. In turn, the uptake of cholesterol would be reflected by normal to high concentrations of cholesterol in HDL, and the cholesterol would be removed from the body pools as HDL is catabolized by the liver and the cholesterol is excreted in the bile. Although there is some conflicting

evidence, it has been felt for many years that chronic alcoholics, usually with cirrhosis, have remarkably lower prevalence and extent of atherosclerosis (Hirst et al. 1965; Howell and Manion 1960). The implications of these data, usually derived from autopsy studies, were not appreciated, nor was interest in alcohol effects on HDL-C renewed until the observations of the past few years.

The evidence for increased blood levels of HDL-C in alcoholics, or in individuals using moderate amounts of alcohol is extensive. However, its significance was not discussed until the recent implication of HDL-C as an antirisk factor for CHD. It was reported that dogs on chronic doses of alcohol showed marked increases in alphaslipoprotein (HDL) cholesterol (Grande et al. 1960). Increased immunoreactive alphaslipoprotein has been demonstrated in alcoholics, especially after excessive alcohol ingestion (Johansson and Laurell 1969; Johansson and Medhus 1974). The increase in alpha-lipoproteins can return to normal within a few weeks if alcohol intake is greatly reduced, suggesting that its elevation may be related to the effect of alcohol on VLDL with increased replenishment of HDL secondary to VLDL lipolysis. In a study of risk factor intervention, it was determined that alcohol intake was directly related to HDL-C concentration (Hulley et al. 1977). Confirmation of the effect of alcohol on HDL-C has come from a number of studies (Bradley et al. 1978; Danielsson et al. 1978; Garrison et al. 1978; Hartung et al. 1980; and Wallerstedt et al. 1977).

Barboriak and coworkers (1979) studied the relationship of HDL-C, alcohol use, and coronary occlusion in heart patients undergoing angiography. HDL-C and alcohol use were negatively correlated with occlusion scores, and alcohol use was positively correlated with HDL-C. It is tempting to speculate cause and effect from the data in this study, i.e., that alcohol use causes increased HDL-C, which in turn causes decreased occlusion.

These presumably beneficial effects of moderate alcohol on HDL-C must be separated clearly from the deleterious effects of excessive alcohol use on the liver and its secondary effects on lipoprotein metabolism. As discussed in an earlier section, alcohol abuse leading to alcoholic hepatitis actually causes abnormal HDL metabolism and very low levels of HDL-C. With the development of alcoholic cirrhosis, and eventually liver failure, persistent derangements in hepatic cholesterol and triglyceride synthesis and in plasma lipoprotein metabolism occur. Since HDL-C is decreased in alcoholic liver disease, it might seem contradictory that the extent of CHD and atherosclerosis is limited in individuals dying from alcoholism and alcoholic cirrhosis. The explanation may reside in the fact that a profound abnormality in lipoprotein metabolism and the low HDL-C associated with alcohol-induced liver disease occur for relatively very brief periods in the life of the alcoholic, whereas sometimes it is decades before alcohol significantly damages the liver. During these years alcohol may exert effects on hepatic triglyceride production and lipoprotein metabolism that lead to high

HDL-C concentrations in blood and consequent protection against CHD.

From our current knowledge of lipoprotein metabolism how might alcohol favorably influence HDL-C? Many studies have demonstrated that the lipolysis of triglyceride-rich lipoproteins (VLDL and chylomicrons) can lead to the transfer of both lipid and protein (particularly apoA-I) to circulating HDL or its precursor, nascent HDL. The apoproteins of both chylomicrons and VLDL change drastically when these particles enter plasma (Schaefer et al. 1978). The chylomicrons and VLDL acquire apoC and apoE, which they later lose during their metabolism. Most chylomicron apoA-I and apoA-II are transferred to HDL, and apoA in plasma is increased with triglyceride flux of either VLDL or chylomicrons.

The precise role of apoA-I in plasma triglyceride clearance is still unknown. Imaizumi et al. (1978) demonstrated that the apoprotein content of triglyceride-rich lipoproteins of the lymph in rats differed substantially from that of liver-derived VLDL circulating in plasma and in fact more closely resembled the apoproteins of plasma HDL. They suggested that apoA-I transported from the intestine in chylomicrons is transferred to HDL in plasma and that this transfer must occur in connection with chylomicron metabolism.

Green et al. (1979), who had previously demonstrated apoA-I synthesis in the rat intestine, also studied this problem in humans. In the urine of patients with chyluria (a condition in which there is a connection between the lymphatic and urinary systems) they found that chylomicrons, VLDL, and HDL all contained apoA-I. The chylomicron fraction also contained apoB, apoA-IV, apoE, apoC, and apoA-II. ApoA-I or apoA-IV are not found in chylomicrons once they enter plasma and are metabolized. When urine chylomicrons were incubated with plasma they lost A-I and A-IV and gained both C and E. The loss of apoA-I and A-IV was dependent on the concentration of HDL in plasma.

A quantitative study of chylomicron metabolism in the rat by Redgrave and Small (1979) led to some interesting calculations in regard to human chylomicron metabolism. Radioactively labeled chylomicrons were administered to normal and hepatectomized rats. After 30 minutes, chylomicrons lost 92 percent of the mass of triglycerides, 77 percent of phospholipids, and 39 percent of protein. Cholesteryl esters of the chylomicrons remained with chylomicron remnants but the phospholipids and protein were transferred to HDL. Approximately 25 percent of chylomicron phospholipids, equal to a 1-hour secretion of a fed rat, was transferred to the HDL phospholipid pool. Extrapolating to man, the fasting pool of HDL phospholipid is about 1.5 grams, and after a fatty meal a human can absorb 50 grams of triglycerides, equal to chylomicrons containing 3 grams of phospholipid. If 25 percent of chylomicron-phospholipid were transferred to HDL, this could account for one-half of the HDL-phospholipid pool and would represent a most important factor in the formation of HDL and in cholesterol homeostasis. These data are confirmed by recent studies indicating that the



phospholipidprotein particles transferred from chylomicrons resemble nascent HDL (Tall et al. 1979).

All of these studies suggest that the increased mass of triglyceride-rich lipoproteins occurring in the blood after alcohol ingestion could be used as a source for increasing the concentration of HDL as the latter is replenished during chylomicron and VLDL metabolism.

To what extent alterations in lipoprotein metabolism induced by alcohol might be beneficial, particularly in reducing the risk of heart disease, is not known. The notion is already current that drinking is beneficial in that it may raise plasma HDL-C, and such a belief could provide justification for increased alcohol use ultimately leading to alcohol abuse and liver disease. However, as Havel (1979) has pointed out, on the basis of our understanding of lipoprotein metabolism it is "premature to include interventions aimed solely at HDL-C in medical practice." He discusses many of the problems that remain to be solved about the meaning of HDL-C and the factors controlling its levels. Among these are the type of HDL (HDL2 or HDL3) that is protective, measurement of particle numbers as well as components of subclasses of HDL, and perhaps most important, the relationship between HDL and other lipoprotein classes, especially VLDL.

### ***Directions for Future Research***

This review has emphasized the effects of alcohol on hepatic and blood lipid and lipoprotein metabolism that occur in the absence or presence of alcohol-induced liver disease. It is important to emphasize the contrasting effects of alcoholic fatty liver and alcoholic hepatitis on blood levels of triglycerides, cholesterol, and HDL-C since there is a possibility that alcohol in moderate amounts may be beneficial in protecting against the development of coronary heart disease, in part by elevating HDL-C. The elevation of HDL-C following moderate alcohol intake is but one reflection of an altered lipoprotein metabolic state that favors protection against the development of atherosclerotic vascular disease. Although the observations of a low incidence of atherosclerosis, coronary heart disease, and myocardial infarction in chronic alcoholics are probably valid, these findings must be tempered by awareness of the severe socioeconomic consequences of alcoholism as well as its effects on liver function, eventually leading to cirrhosis and hepatic insufficiency. Future research on the effects of alcohol on lipid and lipoprotein metabolism should include:

1. The interrelationship of ethanol metabolism to peripheral and hepatic lipid metabolism;
2. Further studies on the mechanism of ethanol-induced hepatocellular injury;
3. The pathogenesis of alcohol-induced fatty liver emphasizing the role of hepatocyte subcellular organelles in lipoprotein secretion

and the importance of imbalances between triglyceride synthesis and lipoprotein formation and secretion;

4. The effects of ethanol on the concentration of blood triglycerides and cholesterol, particularly in relationship to the effects of ethanol on the removal from the blood of dietary fats;
5. The effects of ethanol on hepatic and blood lipoprotein metabolism particularly emphasizing the central role of the liver in lipoprotein metabolism and the secondary consequences of ethanol-induced hepatic injury on lipid and lipoprotein metabolism;
6. The effect of *moderate* alcohol ingestion on blood HDL-cholesterol concentration and the relationship of alcohol to HDL metabolism and its implications for possible protection against atherosclerosis.

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## **Chapter 6**





# **The Relationship of Alcohol and the Cardiovascular System**

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## **Abstract**

Alcohol plays disparate roles in various cardiovascular disorders. Failure to recognize these disparities has, in the past, diverted investigators and has caused delay in understanding this area. Furthermore, the relation of alcohol to each disorder is dependent upon the amount used, and for most conditions, the mechanism of action is probably indirect.

A deleterious effect of large amounts of alcohol upon heart muscle function and biochemical processes has been shown in animals and humans. On the basis of this and other substantial, but circumstantial, evidence, most cardiologists now accept the existence of alcoholic cardiomyopathy, or alcoholic heart disease, as a disorder due directly to the toxicity of alcohol or one of its metabolites. It is likely that chronic use of very large amounts of alcohol is necessary to produce this disorder in susceptible individuals. With abstinence, the condition is largely reversible in its early stages. Cofactors may play a role, although good evidence for such exists only for arsenic and cobalt. Thiamine deficiency causes beriberi, another cardiovascular disorder, and has not been proved to play a role in alcoholic cardiomyopathy. Epidemiological studies suggest that chronic use of three or more ordinary drinks daily is a risk factor for hypertension. Use of smaller amounts of alcohol does not seem to carry such a risk. Mechanisms and a causal relation linking alcohol and hypertension are not established.

Population studies indicate that drinkers are at less risk than nondrinkers for major coronary events. Studies of alcoholics show the opposite. A possible mechanism for an inverse alcohol-coronary relation is the fact that alcohol causes higher blood levels of high-density lipoprotein, a substance inversely related to coronary atherosclerotic disease.

On balance, the adverse cardiovascular risks of acute or chronic use of large amounts of alcohol are clear. For persons who can control their drinking, use of small amounts of alcohol may be beneficial with respect to coronary disease.

## ***Introduction***

The relations of ethyl alcohol to the cardiovascular system and especially to heart disease have excited the interest of investigators and clinicians for well over a century. While much has been learned, there are still few areas of solid knowledge. The clinical, epidemiologic, and physiologic evidence cannot yet be integrated into definitive concepts. Past attempts to generalize have impeded progress in understanding this subject. Some apparent paradoxes disappear if one considers the following concepts.

1. The apparent roles of alcohol in various cardiovascular disorders are disparate. For example, the relation of alcohol to heart muscle disease (cardiomyopathy), hypertension, and the various manifestations of coronary disease has features unique to each condition.
2. The relation of alcohol to a specific cardiovascular disorder is likely to vary with the amount used. For persons who are not alcoholics or who do not have certain cardiovascular disorders there is a safe and possibly beneficial amount.
3. Alcohol most often plays an indirect or partial role in specific cardiovascular disorders. It is best to think of alcohol as a conditioning factor or risk factor in these conditions. Although alcohol is statistically associated with some cardiovascular disorders, a cause-and-effect relation has yet to be proved between alcohol and any cardiovascular condition. Nevertheless, a causal role for alcohol may ultimately be proved in a number of different conditions.

Because of normal concern by the public about the role of habits in health, physicians and other health practitioners must be prepared to advise patients according to the best current knowledge. Recent findings relating alcohol to cardiovascular conditions received wide media coverage and excited much public interest. It is necessary and feasible to give rational advice based on available evidence.

## ***Historical Review***

There have been intellectual digressions in the development of knowledge about the relations of alcohol and heart conditions. Since these digressions have retarded the gaining of insights, this history is worth reviewing.

Some of the great clinicians and pathologists of the 19th and early 20th centuries perceived an association between the regular use of large amounts of alcohol and nonspecific heart disease. Thus the German neurologist Friedreich (1861) described heart enlargement associated with alcoholism. The English physician Walsche (1873) used the term "patchy cirrhosis of the heart," which he felt to be common



among chronic alcoholics. The "Munchener bierherz" (Munich beer heart) was considered a very common condition in the Bavarian capital in the late 19th century. The pathologist Bollinger (1884) described the entity as a nonspecific dilatation and thickening of the heart chambers and also mentioned estimates of an average per capita beer consumption of 432 liters in Munich (compared with 82 liters elsewhere in Germany). In 1893, the great English physician Graham Steell reported a series of 25 cases of alcohol-induced heart disease and stated, "Not only do I recognize alcoholism as one of the causes of muscle failure of the heart but I find it a comparatively common one" (Steell 1893). James MacKenzie (1902) made similar observations and may have been the first to use the term "alcoholic heart disease."

An epidemic of heart muscle disease due to contamination of beer by arsenic occurred in 1900 in England (Gower 1901; Reynolds 1901; Royal Commission 1901*a,b*, 1903). After this epidemic, Steell (1906) adopted the view that the "heart condition" due to use of substantial amounts of alcohol was largely due to arsenic. This change in attitude is an excellent illustration of concentration (by a superb clinician) on a particular aspect of the alcohol-heart disease situation. From 1900 to the late 1920s, there was general doubt that alcohol had a substantial, direct role in heart muscle disease, although the French physician Vaquez took a strong view in favor of such a relation. He published a detailed description (Vaquez 1921) of an illness that undoubtedly would now be called a chronic heart muscle disease with congestive failure (congestive cardiomyopathy).

From the late 1920s to about 1950, the entity "beriberi heart disease" (heart failure due to thiamine or Vitamin B1 deficiency) became the dominant theme in the medical literature concerning the effects of alcohol on the heart. The general interest then rapidly turned back in the 1950s to possible direct effects of alcohol on the heart muscle, separate from or in addition to deficiency states. The terms "alcoholic heart disease" and "alcoholic cardiomyopathy" have been increasingly used, and the existence of such an entity has become more accepted than ever before.

Some feeling has existed since William Heberden's (1786) classical description of angina pectoris that alcohol might be beneficial in coronary disease. Heberden described subjective benefit in angina, the symptom representing perception of inadequate blood supply to the heart muscle. Attempts to demonstrate objective benefit by alcohol for angina have resulted in evidence (Orlando et al. 1976; Russek et al. 1950) that the subjective benefit is due to dulled perception of the discomfort and that the acute blood supply-demand imbalance is not improved or is even worsened by alcohol. Since 1970, largely through epidemiologic studies, considerable interest has arisen in possible relations of chronic alcohol use to both hypertension and coronary atherosclerotic disease. Evidence is increasing that hypertension is more prevalent among heavy drinkers and that coronary disease is more prevalent among abstainers. There has been special interest in

the possible inverse relation of chronic alcohol use and myocardial infarction, commonly known as "heart attack."

### ***Effects of Alcohol on Cardiovascular Function, Biochemistry, and Structure***

Knowledge of the cardiovascular effects of alcohol, especially with respect to the effects of chronic alcohol use, is quite incomplete. Most experimental work on animals and humans has concerned the effects of acutely administered alcohol. In many instances, the results of such investigations cannot be applied directly to the relations of alcohol and chronic disorders. Yet this review would not be complete without considering this evidence, much of which does have implications for disease states. This material is necessarily somewhat technical. The reader primarily interested in relations to cardiovascular disease is advised to skip to Alcohol and Cardiovascular Disease, which includes, at appropriate places, mention of the most relevant material in this section.

#### *Heart Rate, Blood Pressure, and Blood Vessel Tone*

It has long been known that in healthy humans alcohol doses of 30-75 ml (equivalent to two to five ordinary drinks) produce slightly increased heart rate, blood pressure (systolic more than diastolic), and cardiac output (Eliaser and Giansiracusa 1956; Grollman 1930; Juchems and Klobe 1969; Riff et al. 1969). How much of these changes are direct effects of alcohol on the circulation and how much they represent indirect nervous system regulation is unclear. Overall tone of small peripheral blood vessels (peripheral vascular resistance) changes little; blood vessels in the skin dilate (producing the familiar facial flush), but blood vessels in skeletal muscles and internal organs constrict (Fewings et al. 1966; Regan and Ettinger 1979). It has also long been known (Eliaser and Giansiracusa 1956) that doses of alcohol sufficient to produce severe intoxication also produce low blood pressure, slow heart rate, and, ultimately, death from cardiac standstill. Nervous system reflexes are believed to predominate in these effects.

There are suggestions of possible links between alcohol and several abnormal physiological processes in humans that have been implicated in experimental or clinical hypertension. These tentative links include increases in renin and aldosterone (Linkola 1979), which control vascular volume and blood pressure, as well as elevation in cortisone-like hormones to produce a syndrome resembling Cushing's syndrome (adrenocortical hormone excess) that includes hypertension (Ramsay 1979; Smals and Kloppenborg 1977). It has also been suggested that heart rate and blood pressure effects observed in persons using large amounts of alcohol may be due primarily to alcohol withdrawal rather than to direct alcohol effects. Some evidence has been presented

(Wallace 1980) that this may be an important factor in blood pressure elevations seen among heavy drinkers.

### *Effects on Heart Pumping Action*

#### General Summary

The heart muscle effects of alcohol have been explored in numerous studies of normal and diseased humans, intact animals, and isolated animal heart muscle preparations. The results vary according to dose, route, duration, and frequency of administration; parameters measured; and pathologic state of subjects. Most studies indicate that alcohol in sufficient doses decreases the force of heart muscle pumping action (myocardial contractility). The dose required for this effect in humans may be lower if there is clinical evidence of heart muscle disease or if the subject has ingested substantial amounts of alcohol for a long time.

#### Acute Studies

Depressed contraction force has been convincingly demonstrated in isolated heart muscle fibers exposed to alcohol (Gimeno et al. 1962; Spann et al. 1968). Other studies provide evidence of depressed heart muscle contraction in anesthetized dogs (Mendoza et al. 1971; Regan et al. 1966; Webb and Degerli 1965; Webb et al. 1966) and in conscious dogs (Horwitz and Atkins 1974) at blood alcohol levels of 100 mg per 100 ml. Evidence of discharge of the adrenal glands and sympathetic nervous system as a compensatory mechanism has also been demonstrated (Wong 1973), although other investigators (Horwitz and Atkins 1974) could not confirm this.

In normal humans, depressed contraction of the left ventricle, the main pumping chamber of the heart, has been found at blood alcohol levels of 75-250 mg per 100 ml (Mendoza et al. 1971; Newman and Valicenti 1971). These levels could represent very mild to severe intoxication. Similar findings have been demonstrated with various indirect methods such as systolic time interval (Ahmed et al. 1973) and echocardiographic measurements (Delgado et al. 1975) at blood levels of 75-138 mg per 100 ml. This decreased force of contraction was not always associated with decreased cardiac output (Ahmed et al. 1973; Delgado et al. 1975). This led the investigators to suggest that a direct depressant effect of alcohol on the heart muscle brought compensatory mechanisms into play to preserve overall circulatory integrity. Poor correlation of the observed effects with doses of alcohol within the ranges studied (Delgado et al. 1975; Juchems and Klobe 1969) also can be interpreted as evidence for the development of compensatory mechanisms. Still more evidence of physiologic compensation is provided by studies of near maximal cardiac exercise performance that showed little effect of blood alcohol levels of 85 mg per 100 ml to 200 mg per 100 ml in normal humans (Blomqvist et al. 1970; Riff et al. 1969).



The acute depressant effects of alcohol on heart muscle contraction may be more pronounced and may occur with smaller alcohol doses in persons with preexisting heart disease not related to drinking. A study of patients with coronary artery disease (Conway 1968) led to the conclusion that three or four whiskeys profoundly depressed heart muscle. Similar results have been reported with doses of 60 ml of alcohol (equivalent to five 12-ounce cans of beer or 5 ounces of 80 proof whiskey) administered to volunteers with various types of heart disease (Gould et al. 1971, 1972). Analogous evidence is provided by a study of anesthetized dogs to which a standard nonpenetrating blow was given to the chest (Liedtke and DeMuth 1975). Prior administration of alcohol greatly increased the mortality of the blow and decreased the performance of the traumatized heart.

### Chronic Studies

Deleterious effects on heart function have been shown in well-nourished mice fed large amounts of alcohol for only 7 to 10 weeks (Burch et al. 1971). A study of rats that received 25 percent of their calorie intake as alcohol showed a decrease in force of heart muscle contraction (Maines and Aldinger 1967) but no abnormality was seen (Lochner et al. 1969) in the same species given 15 percent of their food intake as alcohol. One study of dogs fed about one-third of their calorie intake as alcohol (Pachinger et al. 1973) showed no functional cardiovascular abnormalities after several months, but another study of dogs fed a like proportion of their calories as alcohol (Regan et al. 1974) showed definite impairment of heart function after 18 months. Thus dose and duration of chronic alcohol use are both important in production of functional cardiac abnormalities in animals. No experiment has yet produced frank congestive failure in well-nourished animals.

There is much evidence that humans with a long history of substantial alcohol intake and without clinical evidence of heart disease often have abnormally functioning heart muscles. This phenomenon, which is considered by many to represent preclinical heart muscle disease, has been demonstrated by physiologic studies (Gould et al. 1969; Limas et al. 1974; Regan et al. 1969) as well as by indirect noninvasive tests (Spodick et al. 1972; Wu et al. 1976). Men may be more susceptible than women to these effects (Wu et al. 1976). The existence of preclinical heart muscle dysfunction in humans and the production of cardiac functional impairment in animals are two of the strongest pieces of evidence supporting the belief that toxic effects of alcohol can produce clinical heart muscle disease (cardiomyopathy) in susceptible persons.

### *Coronary Circulation*

The substantial body of data showing that ethanol adversely affects heart muscle function is not paralleled by similar consistency in known effects of alcohol on the blood supply to the heart muscle (the coronary circulation). In fact, some of the experiments showing acute impairment of heart muscle contractile force (Mendoza et al. 1971; Regan et al. 1969) in humans and dogs showed concomitant increase in coronary blood flow. Ganz (1963) also found evidence suggesting increased coronary blood flow from acute exposure to alcohol. Nevertheless there are experiments that suggest decreased coronary blood flow (Regan et al. 1966; Webb and Degerli 1965) or no effect (Schmittthener et al. 1958; Wendt et al. 1962). Studies of humans with coronary disease who were monitored by electrocardiograph while exercising suggest no benefit or possible worsening of impaired coronary blood flow (Orlando et al. 1976; Russek et al. 1950). It should be kept in mind that responses of normal coronary vessels to pharmacologic agents may differ from responses of diseased vessels, which have limited capacity to dilate.

### *Myocardial Biochemistry*

Little fundamental knowledge exists concerning metabolic defects or abnormalities that could explain functional effects related to alcohol use (Whereat and Perloff 1973). It is not known whether the effects on the heart in humans or animals are due to alcohol itself; some metabolite of alcohol (such as acetaldehyde); associated metabolic consequences of alcohol use (such as low blood magnesium levels, acid-base disturbances, or excess of catechol compounds); or some combination of these. Heart muscle injury cannot be explained by invoking metabolic changes like those that occur in the liver when alcohol is oxidized (Isselbacher 1977), since there is no apparent metabolism of alcohol in muscle cells; the effects of alcohol on the heart must be due to different metabolic processes.

Heart muscle cells use fatty acids as their main energy source, capturing the energy in fatty acids by oxidizing them in the mitochondria. Mitochondria are tiny organelles in which the metabolic building blocks are synthesized into high energy compounds, such as adenosine triphosphate (ATP). There is experimental evidence that alcohol in isolated heart muscle inhibits fatty acid oxidation and causes increased conversion of fatty acids into metabolically inactive compounds in heart muscle cells (Kikuchi and Kako 1970; Lochner et al. 1969). Leakage of heart muscle mitochondrial enzymes (Wendt et al. 1966) and of heart muscle cell ions and enzymes has been shown in humans at blood alcohol levels of 200 mg per 100 ml, even in patients with no clinical evidence of heart disease and no impairment of heart muscle function (Regan et al. 1966, 1969). It has also been suggested that alcohol limits the availability of calcium ion to the contractile protein of heart muscle cells (Rubin 1979). These biochemical effects could translate into a

profound acute effect on both respiration and contractile action of heart muscle cells, with consequent impaired function. However, mechanisms relating *chronic* use of alcohol to heart muscle disease are still unknown.

### *Effects on Heart Muscle Structure*

Enlarged scarred hearts were described as early as 1861 (Friedreich 1861) among some chronic heavy users of alcohol. A number of modern descriptions are available (Alexander 1966*a, b*; Burch et al. 1966; Schenk and Cohen 1970). Grossly, the hearts show increased weight, dilatation of all chambers, scarring of heart muscle, and clots adhering to the inside linings of the chambers. Under the optical microscope there is variation in muscle fiber size, swelling, vacuolization and fatty droplet infiltration in cells, and focal scarring or inflammation. These abnormalities have been observed in very heavy drinkers with no clinical heart disease evident during life (Schenk and Cohen 1970). In these studies of heart pathology the coronary vessels have generally been unobstructed. There has been a report, however, of fibrosis in small branches of the coronary arteries (Factor 1976).

The higher resolving power of the electron microscope allows evidence of damage to be seen in various ultrastructural components including mitochondria, myofibrils, intercalated discs, and the sarcoplasmic reticulum (Alexander 1966*b*; Bulloch et al. 1972; Burch et al. 1966; Mitchell and Cohen 1970). Histochemical studies show an increased accumulation of fat droplets and a decrease in the activity of enzymes of oxidative metabolism. None of the gross, optical microscopic, electron microscopic, or histochemical findings are specific enough to distinguish heart muscle disease in users of large amounts of alcohol from cardiomyopathy in other persons.

Animal experiments have shown production of similar ultrastructural abnormalities with chronic feeding of large amounts of alcohol (Burch et al. 1971; Regan et al. 1974; Segel et al. 1975). The animal experiments, in which all essential nutrients were supplied, give evidence that alcohol toxicity to the heart muscle is not related to associated nutritional deficiency. However, as already mentioned, neither gross cardiac dilatation nor congestive heart failure has yet been produced in animal experiments.

## ***Alcohol and Cardiovascular Disease***

### *Alcoholic Cardiomyopathy*

Much of the evidence described above clearly suggests a direct toxic effect by alcohol or its metabolic products on the structure and function of heart muscle cells. The existence of a chronic disorder due to this direct toxic effect is widely accepted by clinical cardiologists. The



disorder is usually called alcoholic cardiomyopathy, or alcoholic heart disease. More than one basic disorder may be involved. The circumstantial evidence for the existence of this condition is substantial, although there are some who question this (Sereny et al. 1978).

### *Evidence for Alcoholic Cardiomyopathy*

The evidence for alcoholic cardiomyopathy is substantial. First, there are the large number of observations by excellent clinicians and pathologists of the past two centuries. The reports represent various types of practices and populations. So many investigations have seen an association between chronic substantial alcohol use and heart muscle failure that this "anecdotal" evidence cannot be ignored (Alexander 1966a, b; Bollinger 1884; Brigden and Robinson 1964; Burch et al. 1966; Evans 1959, 1961; Hamby 1970; MacKenzie 1902; Pintar et al. 1965; Shugoll et al. 1972; Steell 1893; Vaquez 1921). If this association reflects biased observation (seeing what one looks for), then the majority of currently practicing cardiologists, including the author, have this particular bias.

Further evidence is the fact that longstanding use of substantial amounts of alcohol has been found in a large proportion of patients with unexplained heart disease, often in more than 50 percent (Alexander 1966a; Hamby 1970; Sanders 1963; Shugoll et al. 1972). These patients, surely a diverse group, have evidence of heart muscle disorder without evidence of a specific cause, such as congenital anomaly, valvular disease, hypertension, or coronary artery disease. This situation, which is generally called "cardiomyopathy" or "primary myocardial disease," comprises a variable percentage (usually 2 to 3 percent) of patients hospitalized for severe heart disease. The autopsy percentage is similar.

Alexander (1966a) reported that 80 percent of patients hospitalized at the Minneapolis Veterans Administration Hospital for primary myocardial disease were defined as heavy drinkers compared with 28 percent of patients with other diagnoses admitted to the same medical service. This difference, although impressive, apparently represented a hospital population with a large proportion of substantial alcohol users. On the other hand, the proportion of alcohol users in some series of cardiomyopathy patients has been much lower; Goodwin (1972) stated that "alcohol is certainly not the cause of congestive cardiomyopathy in the majority of patients."

Other evidence consists of a few well-documented case reports. Congestive heart failure developed in one well-nourished patient during a 4-month period when he ingested 12 to 16 ounces (390-518 ml) of Scotch whiskey daily; the clinical abnormality subsided after he ceased drinking (Regan et al. 1969). Other such cases have been reported (Schwartz et al. 1975); many must have been seen and not reported.

An important study (Demakis et al. 1974) documented more frequent regression of clinical abnormality in cardiomyopathy patients who abstained, compared with those who continued to drink.

Other indirect evidence is the documented existence of both acute and chronic peripheral skeletal muscle damage related to alcohol use (Perkoff et al. 1967). Acute myopathy is uncommon but clinically dramatic. Chronic myopathy involves predominantly the proximal girdle muscles (shoulder and hip areas) and is probably relatively common. Data concerning an association with cardiomyopathy are sparse, but a case has been reported (Prasad et al. 1974). Affected skeletal muscles have shown microscopic evidence of inflammation, intercellular edema, and ultrastructural abnormalities of the mitochondria and myofibrils. These abnormalities are similar to the cardiac abnormalities seen in cardiomyopathy (Perkoff et al. 1967; Rubin 1979).

Another example of circumstantial evidence is the observation of heart rhythm disturbances in relation to drinking. Brief drinking sprees in apparently healthy persons can result in premature beats and paroxysmal atrial arrhythmias (especially atrial fibrillation). This phenomenon has been given the colorful name, "holiday heart syndrome" (Ettinger et al. 1976, 1978). More serious arrhythmias are believed to be related to acute alcohol use (Singer and Lundberg 1972). A recent case has been reported of an alcoholic patient in whom ventricular tachycardia could be provoked only after alcohol ingestion (Greenspon et al. 1979).

Perhaps the strongest circumstantial evidence for alcoholic cardiomyopathy are facts already cited in detail: (1) autopsy studies showing abnormalities in large proportions of alcoholics with no clinical evidence of heart disease; (2) acute and chronic interference with heart function and metabolism by alcohol; and (3) structural abnormalities in human and animal heart muscle cells related to alcohol ingestion.

All of this evidence is compatible with the hypothesis that alcohol is either toxic to the heart or is a major conditioning factor in the production of myocardial dysfunction and damage. The evidence summarized in table 1 makes a convincing case for the existence of alcoholic cardiomyopathy.

### *Clinical Features*

Early signs or symptoms are nonspecific electrocardiographic (ECG) changes and rhythm disturbances, often minor. The holiday heart syndrome (Ettinger et al. 1976) following spree drinking has already been mentioned. Nonspecific ST-T variations on the electrocardiogram, as well as arrhythmias, occur among some nonspree drinkers and regress when drinking is reduced or stopped. In a classic article Evans (1959) described T-wave configurations which he considered relatively specific for early alcoholic heart disease, but others (Bashour et al. 1975; Pader 1973; Priest et al. 1966) have not often observed these "characteristic" ECG findings. The prevalence of such early nonspecific evidence of cardiac susceptibility to alcohol is unknown. The likelihood

of progression to chronic myocardial disease is also unknown and probably low. However, it seems reasonable to suppose that these

**Table 1. Evidence in Support of the Entity Called Alcoholic Cardiomyopathy (Alcoholic Heart Disease)**

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1.	Association of drinking and heart muscle disease noted by numerous authorities.
2.	High proportion of chronic users of large amounts of alcohol among patients with congestive cardiomyopathy.
3.	Cases that show convincing evidence of heart muscle dysfunction in relation to episodic drinking.
4.	Acute impairment of heart muscle contractility due to alcohol in humans and animals.
5.	Acute rhythm disturbances related to alcohol in humans ("holiday heart" syndrome).
6.	Impaired heart function in alcoholics without acute alcohol load.
7.	Heart muscle metabolic dysfunction in animals related to acute alcohol load.
8.	Alcohol-produced heart muscle cellular abnormalities in animals.
9.	Autopsy evidence of heart muscle damage in alcoholics with no history of clinical heart disease.
10.	Well-documented acute and chronic skeletal muscle syndromes due to alcohol.

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persons represent a high-risk group, and there is evidence that reversibility is maximal at early stages of alcoholic heart disease. Therefore clinicians should be alert to recognizing such individuals.

The late clinical picture, a chronically weakened and dilated heart, is described in several excellent reports (Alexander 1966a; Brigden and Robinson 1964; Burch et al. 1966; Parker 1974; Pintar et al. 1965; Sanders 1963). Congestive heart failure, chronic rhythm disturbances, conduction abnormalities on the ECG, and high incidence of embolic complications (i.e., blood clots obstructing circulation) are characteristic. Although the development is usually insidious, a number of patients seem to have an acute onset of severe heart failure, and do not come to medical attention before the late stage has been reached. Even at this point some patients show partial regression, but many progress inexorably despite abstinence from alcohol and optimal medical therapy. Except for the relation to alcohol use, this clinical picture cannot be distinguished from chronic congestive cardiomyopathy of any cause.

### *Diagnosis*

The diagnosis of alcoholic cardiomyopathy is always presumptive. This fact, plus the known difficulty in obtaining accurate drinking histories, leaves clinicians with the amorphous diagnostic tools described below.



## A Compatible Drinking History

Little is known about the minimum amount and duration of regular alcohol use that may lead to cardiomyopathy. The amount seems likely to be large, especially in the absence of another type of heart disease. The prevalence is probably low, even among users of large amounts of alcoholic beverages, but estimates are guesswork. Cardiomyopathy is thought to be distinctly less common than liver damage, and the two do not ordinarily coexist. This fact probably reflects (1) the importance of individual susceptibility factors, genetic and environmental, in the development of both types of disorders; and (2) the relatively low prevalence of both liver and heart disease among regular substantial drinkers. However, a statistical artifact may be involved, as the existence of one major illness with a high mortality rate tends to preclude the eventual clinical emergence of another.

## The Exclusion of Other Causes of Heart Disease

This is clearly necessary but it is intellectually bothersome because there is no logical reason that a person might not have both alcoholic heart disease and another type of heart disease. Existence of some other type of heart disease might actually predispose a person to heart muscle damage by alcohol.

### *Acute Worsening with Substantial Drinking.*

## Consistent Pathologic Evidence

Most authorities do not recognize nize specific pathologic changes by either optical or electron microscopy.

## Problems

There are no specific symptoms, signs, tests, or pathologic findings. The diagnosis of alcoholic heart disease must rest upon a high clinical index of suspicion and the skillful interpretation of nonspecific evidence.

### *Other Clinical Features*

## Treatment and Prognosis

Abstinence from alcohol is the mainstay of treatment. Rest, digitalis, diuretics, antiarrhythmic drugs, and other measures appropriate to the individual's clinical picture should be employed. The recovery rate is good in early disease with abstinence. Even with advanced disease a marked degree of recovery is possible (Demakis et al. 1974; Reeves et al. 1978; Schwartz et al. 1975), although there is a high death rate from congestive heart failure, sudden death due to arrhythmias, and embolism.

## Risk Factors and Cofactors

Aside from the possible greater susceptibility of males (Wu et al. 1976), little is known about the reasons for individual susceptibility to alcohol's toxic effects on the heart. It seems fairly certain that alcohol itself is the major toxin, but a possible role for other constituents of wine, beer, or certain types of distilled spirits may exist.

The concept of synergistic toxicity to the heart by alcohol and other cofactors is supported by two well-documented historical episodes. The first was a major epidemic at the turn of the century in and near Manchester, England, due to accidental contamination of beer by arsenic (Gower 1901; Reynolds 1901; Royal Commission 1901a, b, 1903). This episode caused a major intellectual digression in the development of the concept of alcoholic heart disease. The second occurred 65 years later in several locations in North America and in Belgium and was due to the use of cobalt as a foaming agent in beer (Alexander 1968, 1969; Kesteloot et al. 1968; McDermott et al. 1966; Morin and Daniel 1967; Sullivan et al. 1969). In both epidemics there was an abrupt severe illness characterized principally by acute heart muscle failure in chronic drinkers of large amounts of beer. Those who recovered appeared able to resume their beer-drinking habit without apparent harm. The amounts of cobalt and arsenic involved were insufficient by themselves to account for the heart damage. Although no biochemical mechanisms were established, these events strongly suggest synergistic toxicity (the enhancement of the effect of one substance by the presence of another chemical).

The parallels between the arsenic and cobalt beer episodes make it likely that other metals and chemicals can act synergistically with alcohol to produce cardiomyopathy. Thus it seems reasonable that multiple factors may be involved in many instances of cardiomyopathy. Possibilities include iron, selenium, copper, and drugs with heart-damaging properties (emetine, adriamycin, and tricyclic antidepressants are a few). Furthermore, it is known that myocarditis occurs with many viral illnesses and the possibility exists that residual heart damage acts as a cofactor in other heart muscle diseases. In fact a possible synergistic role between almost any type of heart muscle impairment and alcohol is a reasonable hypothesis. A similar role of vitamin or nutritional deficiencies may exist, but this also is not established. (See discussion below of thiamine deficiency—beriberi.)

## Differences Between Persons Considered To Be Alcoholic and Others

Most reported cases of alcoholic cardiomyopathy have involved alcoholics or problem drinkers. The types of populations involved have ranged from the medically indigent to the affluent, overnourished, professionally successful private patients gleaned from Evans' Harley Street practice (Evans 1959, 1961). Reasoning by analogy from knowledge about the dose of alcohol that is toxic to the liver, Regan

(Regan and Ettinger 1979) estimated that 80 grams of ethanol a day (equivalent to 9 to 10 ounces of 80 proof whiskey) over a period of years is necessary to produce cardiomyopathy. If this estimate is correct, it seems unlikely that drinkers without a drinking problem are at risk of permanent cardiac damage. Arrhythmias may occur at lower doses of alcohol and with shorter exposure periods. Transient rhythm disturbances may well be the commonest clinical expression of alcohol's cardiac toxicity, especially in persons not obviously addicted to alcohol. There are no data, however, about the incidence of this phenomenon.

### *Cardiovascular Beriberi*

For several decades, the concept of cardiovascular beriberi dominated thinking about the relation of alcohol to heart disease. Although the condition was well known previously, the classical detailed description by Aalsmeer and Wenckebach (1929) clearly defined a clinical picture of heart failure with high cardiac output. Beriberi in persons in the Orient who subsisted on polished rice was due to thiamine (Vitamin B1) deficiency. Because some cases in Western countries had a similar clinical picture and responded well to thiamine, it was assumed (Keefer 1930) that most heart failure in heavy drinkers was caused by associated nutritional deficiencies. In the 1960s (Blacket and Palmer 1960) and 1970s (Kozam et al. 1972), high-output cardiovascular beriberi was studied by modern physiologic techniques in a few cases. These patients showed remarkably high cardiac outputs at rest, among the highest ever measured. The major cardiovascular physiologic consequence of thiamine deficiency in most appeared to be dilatation of peripheral, small blood vessels with the creation, in effect, of a large arteriovenous shunt. Some responded remarkably rapidly (hours to days) to thiamine, with apparent complete recovery. The clinical observations of Aalsmeer and Wenckebach were confirmed.

In Western countries, the cases presumed to represent vitamin-deficiency-induced heart failure all used large amounts of alcohol (Keefer 1930). It gradually became apparent that only a minority fit the rice beriberi picture. Many if not most had good nutritional state, responded poorly if at all to thiamine administration, and had low-output heart failure with predominant left ventricular failure (in contrast to the right ventricular failure so evident in Oriental beriberi) (Weiss and Wilkins 1937). A widely held view was that in longstanding thiamine deficiency, chronic myocardial damage occurred that no longer responded to thiamine (Blankenhorn 1945; Blankenhorn et al. 1946). An instructive case reported by Robin and Goldschlager (1976) demonstrated two syndromes in sequence in the same patient. He first had a high cardiac output state that responded to thiamine, then somewhat later developed a low cardiac heart failure that was unresponsive to thiamine. This was interpreted as representing beriberi followed by alcoholic cardiomyopathy.



It became the prevalent view (Jones 1959) that chronic thiamine deficiency as a cause of congestive cardiomyopathy has been poorly documented, but that thiamine deficiency may be a conditioning factor in some cases. Thiamine deficiency is probably, at most, a contributory factor in the "atypical" cases of beriberi. Blacket and Palmer (1960) stated it well: "It (beriberi) responds completely to thiamine, but merges imperceptibly into another disease called alcoholic cardiomyopathy, which does not respond to thiamine."

### *Alcohol and Hypertension*

Strong epidemiologic evidence exists that regular use of large amounts of alcohol is associated with a substantially higher prevalence of hypertension. On the other hand, persons who use small amounts of alcohol, up to the amounts contained in one or two drinks daily, seem to fare slightly better than nondrinkers with regard to blood pressure measurements. This possible environmental link to a common serious condition is of both theoretical and practical importance.

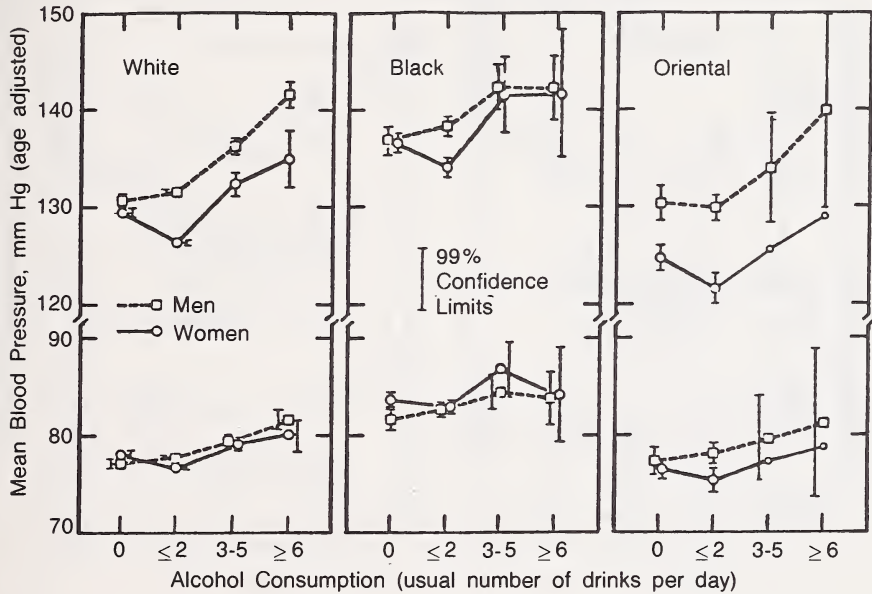
The reports (Beevers 1977; Clark et al. 1967; D'Alonzo and Pell 1968; Dyer et al. 1977; Kannell and Sorlie 1974; Mathews 1976; Myrhed 1974; Ramsay 1977) of an alcohol-blood pressure link represent varied populations. By far the largest study (Klatsky et al. 1977*b*, 1979*b*) used data gathered at checkup examinations given at the Kaiser-Permanente Health Care Program in Northern California. These data showed a statistically strong association between blood pressure and known drinking habits of 83,947 men and women of three races (figure 1). Persons were classified by questionnaire responses as nondrinkers or according to usual daily number of drinks: two or fewer per day, three to five per day, or six or more per day. Among men of all three races mean blood pressures among those who took two or fewer drinks per day were generally similar to those of nondrinkers. Women of all three races who took two or fewer drinks daily had mean pressures slightly lower than nondrinkers. Men and women of all races who took three or more drinks daily had higher systolic and diastolic blood pressures than either nondrinkers or persons who took two or fewer drinks daily. This trend of increasing mean blood pressure with increasing alcohol use continued in whites and Orientals up to regular daily consumption of six to eight drinks daily but then leveled off (i.e., pressures of persons taking more than nine drinks daily were not higher than those taking six to eight drinks daily). Among black men and women the blood pressure-drinking association did not progress beyond the category of three to five drinks per day. After cross-classification this relation proved to be independent of smoking, coffee use, salt use, blood group, educational attainment, and adiposity (height/weight index). Figure 2 shows the cross-classification with adiposity, a trait related to blood pressure in this study population as well as others. Figure 3 shows the cross-classification with the habit of salting food before tasting it, which, interestingly, was not related to blood pressure in this study population.

The difference in mean blood pressure in the Kaiser-Permanente study translated into a doubled prevalence of hypertension (defined as blood pressure of 160/95 mm Hg or higher) in white men and women who took six or more drinks daily compared with nondrinkers or users of two or fewer drinks daily. Among black men and women, the prevalence of hypertension (160/95 mm Hg or higher) among users of three or more drinks daily was increased by approximately 50 percent (figure 4). The doubled prevalence among the white heavier drinkers was quite similar to the findings in other studies (Conway 1968; Kannell and Sorlie 1974) in which the methods of classifying data allowed comparison.

In view of agreement among various studies, some type of association between alcohol use and blood pressure is established. However, various types of indirect association have not been ruled out. These include (1) psychosocial stress as an underlying factor for both hypertension and use of large amounts of alcohol, (2) a common hereditary predilection both for use of alcohol and hypertension, (3) other environmental factors such as dietary habits, and (4) alcohol withdrawal. An early withdrawal state is possible among some users of large amounts of alcohol who might tend to sober up for health examinations; alcohol withdrawal is associated with increased heart rate and blood pressure in some heavy drinkers (Wallace 1980).

The blood pressure elevations among heavier drinkers, whether direct or indirect, could be a temporary effect that disappears, at least in part, with reduced drinking. The study of D'Alonzo and Pell (1968) among du Pont employees supports this possibility. On the other hand, there was a residual increase in hypertension prevalence among presumably abstinent alcoholics in the du Pont workers. The failure of the drinking-blood pressure relation to progress at very high drinking levels (Klatsky et al. 1977*b*) is not explained. It has been suggested (Klatsky et al. 1977*b*; Ramsay 1979) that this apparent plateau in the dose-response curve could be due to cirrhosis or cardiomyopathy among the heaviest drinkers. This phenomenon could account for the failure to find a disproportionate amount of hypertension in some studies of alcoholics (Regan et al. 1969; Wu et al. 1976).

Figure 1. Association Between Blood Pressure and Drinking Habits<sup>1</sup>



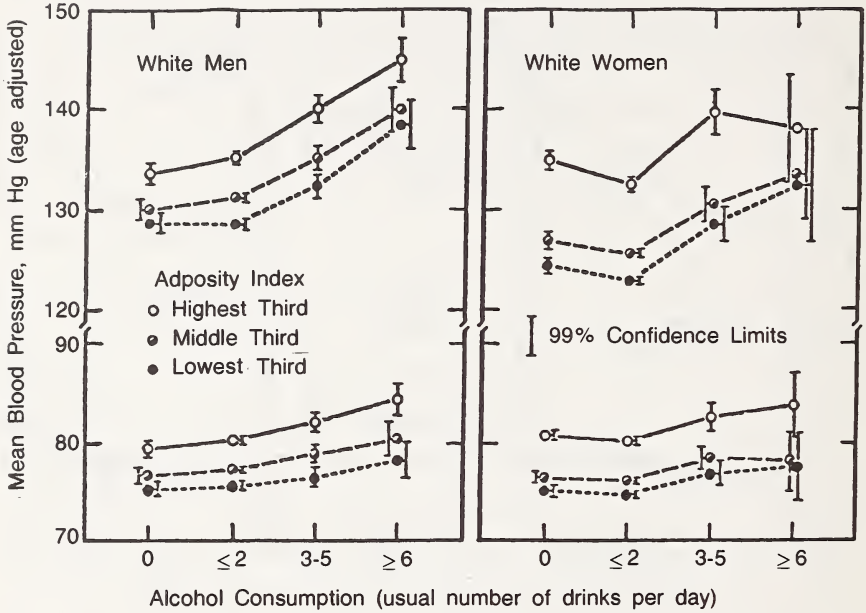
SOURCE: Reprinted by permission of the *New England Journal of Medicine* (296:1194-1200, 1977).

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<sup>1</sup> Mean systolic blood pressures (upper half of figure) and mean diastolic blood pressures (lower half of figure) of white, black, or Oriental men and women with known drinking habits. Small circles represent data based on less than 30 persons.



Figure 2. Association Between Blood Pressure, Adiposity, and Drinking Habits<sup>1</sup>

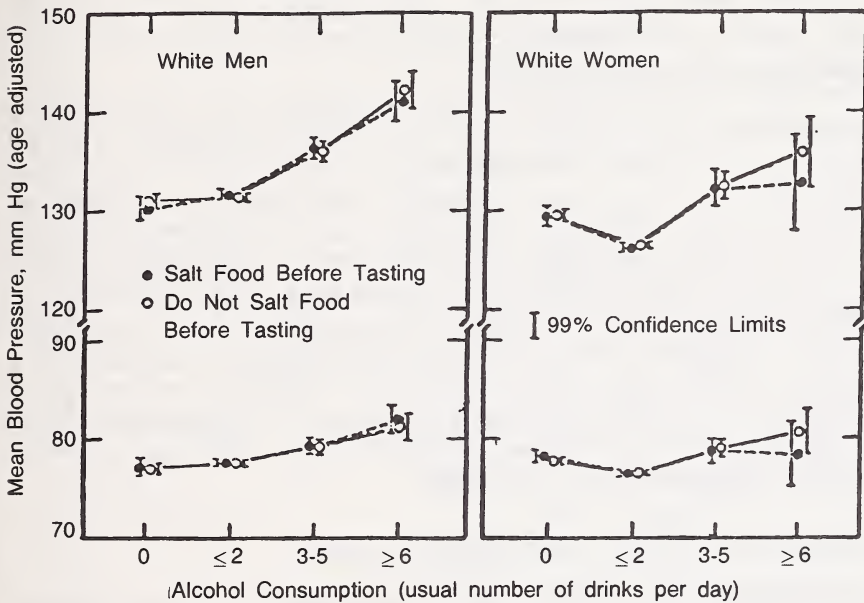


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<sup>1</sup> Mean systolic blood pressures (upper half of figure) and diastolic blood pressures (lower half of figure) of white men and women with known drinking habits, according to Quetelet's Index ( $(Wt/Ht^2 \times 100)$ ) by tertiles.

Figure 3. Lack of Association Between Blood Pressure and Food-Salting Habits in Persons With Known Drinking Habits<sup>1</sup>



SOURCE: Reprinted with permission from Klatsky, A.L.; Friedman, G.D.; and Siegelau, A.B. Alcohol and hypertension. *Comprehensive Therapy* 4:60-68, 1978.

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<sup>1</sup> Mean systolic pressures (upper half of figure) and diastolic blood pressures (lower half of figure) of white men and women with known drinking habits, according to usual salt use habit.

A physiologic mechanism is not established. As already discussed, the effects of acutely administered alcohol on blood pressure do not provide a ready explanation. Evidence is very limited about pathophysiologic actions of chronic substantial drinking that could account for blood pressure elevations. There has been speculation about a chronic "hypermetabolic state," chronic corticosteroid excess (Rees et al. 1977; Smals and Kloppenborg 1977), and action through the renin-angiotensin system (Linkola 1979).

In view of the uncertainty about the nature of the alcohol-blood pressure association and the absence of a proven mechanism, a causal relation is not proven. Nevertheless, the possibility of a true direct association is strong enough to warrant consideration of alcohol use when evaluating hypertension. It seems prudent for health practitioners to advise hypertensive patients who take three or more drinks a day (35 ml or more of absolute alcohol) to reduce their intake. No change in habit seems necessary for hypertensive patients taking the equivalent of one or two drinks per day. Elevated blood pressure may itself be a clue to a substantial drinking habit; in the Kaiser-Permanente study (Klatsky et al. 1977*b*) approximately one-third of middle-aged (40-59 years) white men with blood pressure 160/95 or higher reported ingestion of three drinks or more a day.

### *Alcohol and Coronary Atherosclerotic Disease*

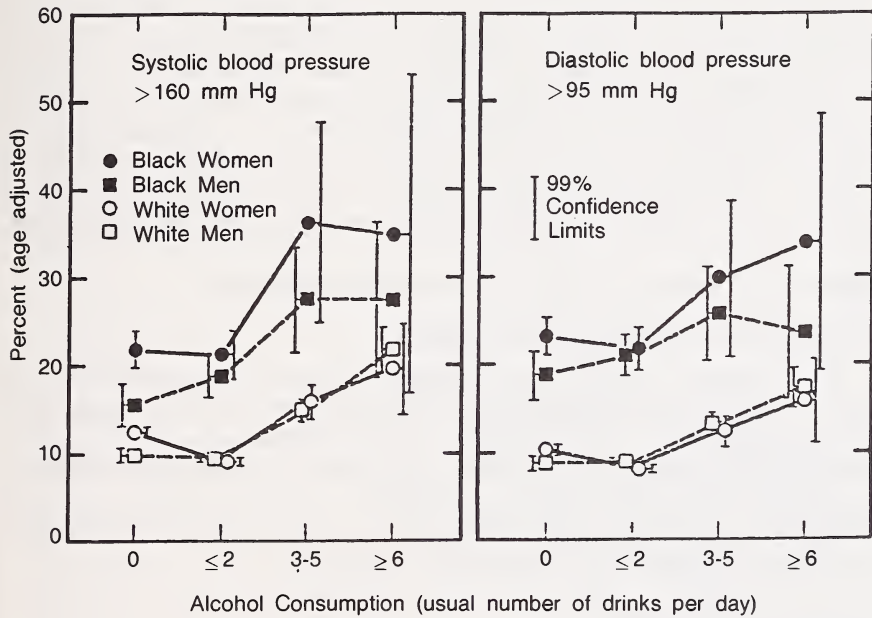
In coronary atherosclerosis the factors involved in the production of the underlying occlusive process are not identical to those that immediately provoke symptoms or clinical events. Furthermore, present knowledge suggests that the role of alcohol should be considered separately for each of the three major clinical expressions of the condition: angina pectoris, acute myocardial infarction, and sudden death.

#### *Angina Pectoris*

Heberden's classic description of angina (1786) included the statement that ". . . wine and spiritous liquors afford considerable relief." Over the ensuing two centuries it was widely presumed (Levine 1951; White 1931) that alcohol was a coronary vasodilator. However, studies of exercise performance ability using electrocardiographic evidence of inadequate coronary blood flow show either no benefit (Russek et al. 1950) or, with doses of 65-320 ml of alcohol, decreased exercise performance ability (Orlando et al. 1976). However, in contrast to the effects of other types of ingested foodstuffs, the *perception* of ischemic discomfort with exercise—anginal distress—did not occur sooner when alcohol was given. This evidence strongly suggests that it is unwise for angina patients to use alcohol as an immediate preventive measure before exercise.



Figure 4. Prevalence of Hypertension as a Function of Alcohol Consumption and Race<sup>1</sup>



SOURCE: Reprinted with permission from the *New England Journal of Medicine* (296:1194-1200, 1977).

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<sup>1</sup> Percentage of white and black men and women with systolic blood pressures 160 mm Hg (left) and diastolic blood pressures 95 mm Hg (right), according to current drinking habits.

Attempts to study coronary blood flow in relation to acutely administered alcohol have yielded conflicting findings (Ganz 1963; Mendoza et al. 1971; Regan et al. 1969; Schmitthenner et al. 1958; Webb and Degerli 1965; Wendt et al. 1962). Furthermore, the acute effects of doses of 30-75 ml of alcohol administered to humans (slight increase in heart rate, blood pressure, and cardiac output) (Eliaser and Giansiracusa 1956; Grollman 1930; Juchems and Klobe 1969; Riff et al. 1969) may affect the occurrence of myocardial ischemia independent of any possible action of alcohol on the coronary circulation itself. Thus an ambiguous relation exists between alcohol ingestion and angina pectoris due to coronary atherosclerotic disease. Subjective benefit is probably not related to concurrent improvement in myocardial oxygen supply, but presumably is due to anesthetic or tranquilizing effects of alcohol. Alcoholic beverages should not be recommended as a substitute for nitroglycerine as protection against effort-induced angina.

### *Myocardial Infarction and Coronary Disease Mortality*

#### *Evidence from Epidemiologic Studies*

The relation of alcohol consumption to myocardial infarction and death from coronary disease has aroused much recent interest and some controversy. It is useful to briefly review some of the major studies. They may be divided into two general types: population studies, in which drinkers report their consumption (not usually of large amounts of alcoholic beverages); and studies of alcoholics or problem drinkers, generally in treatment or rehabilitation programs.

#### *Population Studies*

An early report from a study of Western Electric employees in Chicago (Paul et al. 1963) showed no association between alcohol use and coronary events. The Los Angeles Heart Study also found no drinking-coronary disease association (Chapman et al. 1974) although former drinkers had a slightly higher incidence of disease. It is not clear from these reports whether the data were controlled for cigarette smoking, a well-established predictor of coronary events and a strong correlate of alcohol use. The Framingham Heart Study reported data (U.S. National Heart Institute 1966) showing a slight but statistically insignificant inverse relation (drinkers at less risk) between use of 30 or more ounces of alcohol per month and myocardial infarction, even without apparent control for smoking.

In a population study well controlled for smoking and other established coronary risk factors (Friedman et al. 1974), there was a statistically significant inverse relation of alcohol use and heart attack among members of the Northern California Kaiser-Permanente Health Care Program (Klatsky et al. 1974, 1976). A slightly inverse, but not statistically significant, relation between drinking and sudden cardiac death (Friedman et al. 1975; Klatsky et al. 1979b) was also found in the

Kaiser-Permanente study. Almost all of these sudden deaths were attributable to coronary disease. In the Kaiser-Permanente studies the largest difference in coronary risk was the difference between current nondrinkers (including past drinkers) and light to moderate drinkers (two or fewer drinks per day), but the inverse drinking-coronary relation was slightly progressive up to users of six or more drinks per day. There was no significant relation, positive or negative, between reported past heavy drinking and heart attack.

In a study of Japanese men in Honolulu a statistically significant inverse relation was found between drinking and both myocardial infarction and coronary mortality (Blackwelder et al. 1980; Yano et al. 1977). The men drank mostly beer and few drank more than 30 ml of absolute alcohol daily, but the inverse drinking-coronary disease relation was progressive with increasing alcohol use.

A report from the Boston Collaborative Drug Surveillance Program (Stason et al. 1976) showed a slight inverse relation between alcohol use and nonfatal myocardial infarction. Another recent study in Boston (Hennekens et al. 1978) showed an inverse relation between alcohol use and death from coronary disease. In a later report (Hennekens et al. 1979), the relation was shown independently for users for beer, wine, or distilled spirits. A second study from the Kaiser-Permanente Program was recently presented (Klatsky 1980; Klatsky et al. 1979c) showing a significantly lower hospitalization incidence for coronary disease among drinkers than among nondrinkers. These data were derived from followup of four matched groups of 2,015 persons each, nondrinkers and users of two or fewer, three to five, and six or more drinks per day. Among these 8,060 persons there was again a slightly progressive inverse relation between drinking up to six or more drinks per day and heart attack, but, as in the earlier Kaiser-Permanente study, the largest difference in heart attack risk was between nondrinkers and those who had two or fewer drinks daily.

### *Studies of problem drinkers and alcoholics*

On the other hand, a number of studies among problem drinkers or alcoholics have presented data showing a *higher* risk of myocardial infarction or coronary death among these persons. These include reports from studies of du Pont employees (D'Alonzo and Pell 1968), the State of California Alcoholic Rehabilitation Program (California State Department of Public Health 1961), alcoholics in a rehabilitation program in Toronto (Schmidt and deLint 1972), Swedish Temperance Board registrants (Wilhelmsen et al. 1973), problem drinkers in the Chicago Peoples Gas Company in Chicago (Dyer et al. 1977), and heavy drinkers (five or more drinks per day) among Western Electric Company employees in Chicago (Dyer et al. 1977).

Among these studies, the first three are comparisons between groups not controlled for important coronary risk factors including smoking. Only the Swedish Temperance Board registrants showed a



statistically significant increased risk of both nonfatal myocardial infarction and coronary death with control for smoking and other coronary risk factors. The two Chicago studies (Dyer et al. 1977) were controlled for smoking; the Peoples Gas Company study showed a significantly increased coronary mortality risk among 38 problem drinkers (in 1,233 white men examined) and the Western Electric study showed a slight but statistically insignificant increased mortality risk among 117 heavy drinkers (in 1,899 white males).

Thus most of the population studies suggest that drinkers suffer fewer major coronary events while the studies of alcoholics show the opposite. It is possible that large amounts of alcohol have effects in coronary disease quite different from those of smaller amounts, but other explanations for this discrepancy are more likely.

Possible explanations for a spurious association in the population studies include these alternatives: (1) former drinkers, a subset of the nondrinkers in several of the studies, may be at especially high coronary risk; (2) there may be indirect association through ethnic factors, psychological traits, or other unknown risk factors. The second hypothesis would require the existence of a trait predisposing to coronary disease in larger proportions of nondrinkers than drinkers. There are more numerous and more convincing explanations for a possible spurious association between very heavy drinking and coronary events.

1. Indirect relation of very heavy drinking and coronary events through established coronary risk factors is almost certain. Both hypertension and cigarette smoking are strong predictors of coronary events and are related to alcohol use. The association between smoking and drinking is especially strong among users of large amounts of alcohol (Klatsky 1980; Klatsky et al. 1977a, 1979a; Schmidt and deLint 1972). This relation can easily be seen in figure 5, which shows the alcohol use-myocardial infarction relation in the Kaiser-Permanente study (Klatsky et al. 1974) among persons who never smoked and among established smokers.
2. Indirect relation may exist through other possible risk factors, such as psychosocial stress, which could be related to both heavy drinking and heart attack.
3. Possible erroneous diagnosis of cardiac death may be made among alcoholics who die of noncardiac causes (Dyer et al. 1977).
4. Possible erroneous diagnosis of coronary disease among alcoholics who die of other cardiac conditions, such as alcoholic cardiomyopathy, may also be made.

### Other Evidence

In the first half of this century there were a number of reports (Cabot 1904; Hultgen 1910; Leary 1931; Parrish and Eberly 1961; Wilens 1947)

of an apparent inverse relation between chronic substantial alcohol use and atherosclerotic disease, including coronary disease, diagnosed at autopsy. However, this was dismissed by some (Parrish and Eberly 1961; Ruebner et al. 1961) as a statistical artifact, i.e., that the premature deaths of many alcoholic persons might preclude the development of atherosclerotic vascular disease. Important work reported by Barboriak and colleagues (1977, 1979) showed that among 900 patients examined by coronary arteriography (X-rays of coronary vessels), drinkers had significantly less atherosclerotic occlusion than nondrinkers, although the drinkers smoked more. Recent experimental data (Clarkson 1980) concerning monkeys fed 36 percent of their calorie intake as alcohol indicate that alcohol at this level apparently reduces the development of experimental coronary atherosclerosis.

### Possible Explanations for the Inverse Alcohol-Coronary Disease Relation

As already mentioned, indirect associations with psychological traits, dietary habits, ethnic factors, or unknown confounders could explain relations of drinking habits with coronary disease. The emergence of a plausible mechanism for a protective effect of alcohol in coronary disease increases the possibility that such an effect exists. The mechanism is based on the observation that alcohol raises high-density lipoprotein cholesterol (HDL) levels in blood (Castelli et al. 1977; Hulley 1980; Kuller 1980; Rhoads, Kagan, and Yano 1976). Elevated HDL is inversely related to coronary atherosclerotic disease (Castelli 1980; Goldbourt and Medalie 1977; Rhoads, Gulbrandsen and Kagan 1976) and may have a protective role by aiding in removal of cholesterol from the body or by retarding the formation of atherosclerotic plaques. The effect of alcohol in raising HDL levels is generally proportional to the amount regularly taken (Hulley 1980). Alcohol-induced HDL elevations decrease in days to weeks when drinking is stopped (Hulley 1980; Kuller 1980). There is evidence that the site of action of alcohol's influence on HDL is the liver; in some very heavy drinkers with acute or severe liver disease the HDL levels may be very low (Kuller 1980; Sabesin 1980).

There is much research in the area of HDL cholesterol and its relation to coronary disease, alcohol use, and other factors. While the evidence that alcohol and HDL are linked is growing rapidly, the hypothesis that this link causes a protective effect by alcohol against coronary disease is not firmly established at this time.

Alcohol also affects other blood lipids. It raises blood triglycerides markedly in some persons, but this is limited to a fraction of drinkers and is not considered important in atherogenesis (Castelli et al. 1977). Alcohol may also lower the levels of the highly atherogenic low-density lipoproteins (LDL) (Castelli et al. 1977).

It is also possible that alcohol may protect against major coronary events by some other mechanism besides prevention of atherosclerotic

occlusion. Although this has not been studied extensively, evidence for such an action has been reported (Hartz et al. 1979). Such protection might be mediated by inhibition of platelet aggregation (Haut and Cowan 1974).

This author feels that on balance the evidence from the population studies and studies of atherosclerotic occlusion strongly suggests a true inverse relation between light to moderate drinking and both myocardial infarction and coronary disease mortality. A strong possibility exists that this protective effect is through the HDL mechanism, but substantially more knowledge about the mechanisms involved is needed before this can be regarded as established. The relation of heavier drinking to coronary events is unclear and is probably different in some important respect from the relation of low-dose alcohol use. It is not possible to define "moderate" and "heavy" drinking with any precision, but it appears likely that use of up to 2 ounces (65 ml) of absolute ethyl alcohol daily places people at or close to the lowest coronary risk.

### *Alcohol and Other Cardiovascular Disease*

#### Stroke

A positive relation between drinking and stroke incidence has been reported (Blackwelder et al. 1980; Castelli 1980; Kagan 1980; Katsuki 1971; Klatsky 1980; Klatsky et al. 1979c). The relation is stronger for hemorrhagic than for thrombotic stroke (Blackwelder et al. 1980; Klatsky et al. 1979c) and is felt to be not entirely explained by the association of both drinking and stroke with hypertension. A bleeding tendency due to alcohol has been implicated (Kagan 1980) as a possible additional explanation.

#### Aortic and Peripheral Vessel Atherosclerosis

There is little epidemiologic evidence to suggest a relation to alcohol use (Klatsky 1980; Klatsky et al. 1979c).

#### Noncoronary Atherosclerotic Disease

An unusual form of angina pectoris, known as Prinzmetal variant angina, is widely believed to be related in some patients to reversible spasm of large coronary vessels (Rosenblatt and Selzer 1977). Although alcohol has been reported to be one of the pharmacologic agents that can induce this phenomenon (Fernandez et al. 1973), the association has not been widely observed.

Regan (Regan et al. 1975) reported a number of cases of myocardial infarction among alcoholics with no evidence of atherosclerotic or thrombotic occlusion. He postulated a mechanism of external constriction of coronary vessels by scarring due to alcoholic cardiomyopathy. Myocardial infarction without atherosclerosis is a poorly understood

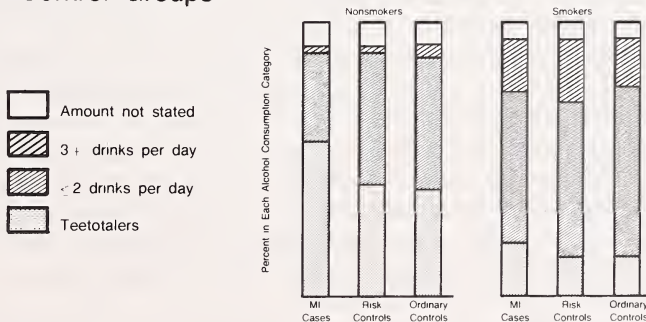


event that also occasionally occurs in nonalcoholics (Rosenblatt and Selzer 1977).

Table 2. Disparate Relations of Alcohol and Cardiovascular Conditions

	Apparent Relation to Use of Alcohol	
	Small Amounts	Large Amounts
Arsenic (As) beer drinkers' disease	None	Synergistic myocardial toxicity of As, alcohol
Cobalt (Co) beer drinkers' disease	None	Synergistic myocardial toxicity of Co, alcohol
Beri-beri	None	None (cause is thiamine deficiency)
Alcoholic cardiomyopathy	None	Direct myocardial toxicity in susceptible persons
Hypertension	None or slightly inverse (less hypertension)	Direct (More hypertension)
Atherosclerotic coronary disease	Inverse (less disease)	Conflicting evidence
Stroke	?	Direct (stronger for hemorrhagic than thrombotic stroke)
Venous conditions	None	Direct

Figure 5. The Relation of Alcohol Consumption to Cigarette Smoking in Myocardial Infarction (MI) Patients and Two Control Groups



Source: *Annals of Internal Medicine* 81:294-301, 1974 (reproduced by permission) Copyright, 1974, *Annals of Internal Medicine*.

Note: Both control groups were matched to 464 MI patients, one by one, for age, sex, and race. One group (risk controls) was matched also for seven coronary risk factors. The nonsmokers included 113 myocardial infarction patients, 129 risk controls, and 179 ordinary controls. The established smokers included 185 myocardial infarction patients, 192 risk controls, and 120 ordinary controls.

### Other Conditions

Substantial alcohol use has been reported to be associated with a higher incidence of venous conditions (Klatsky 1980), such as phlebitis and varicose veins. Heavy maternal drinking is associated with congenital anomalies of the heart (septal defects and patent ductus arteriosus) in offspring (Noonan 1976).

Table 2 summarizes the disparate relations of alcohol use and cardiovascular conditions. A recent report on hospitalization incidence in a large number of persons of various alcohol habits (Klatsky 1980; Klatsky et al. 1979c) demonstrated this disparity in a single cohort. The heaviest drinkers fared worst, due to a higher risk of hypertension, stroke, congestive failure, arrhythmias, venous conditions, and cardiomyopathy. Moderate drinkers (two or fewer drinks per day) fared best with respect to overall incidence of hospitalization for cardiovascular causes. Nondrinkers fared substantially worse than the moderate drinkers, primarily because of a higher incidence of coronary heart disease. Hospitalizations for coronary events showed a pattern distinctly different from that for any other cardiovascular condition, with nondrinkers at significantly greater risk.

### ***Public Health Aspects of Alcohol and Cardiovascular Diseases***

The American public, aware of advances in knowledge in the alcohol-cardiovascular area, expects sound advice based on current knowledge, although it is probably easier to counsel individual patients than to formulate general pronouncements. Most health professionals would probably agree on a few basic facts: (1) There is substantial evidence that use of large amounts of alcohol carries heavy medical and social risks. The medical risks include cardiovascular and noncardiovascular disorders. (2) The threshold dose for possible harmful effects of alcohol is not known and probably varies from person to person. (3) Many persons should not drink at all—those with a history of a drinking problem or at special risk of a drinking problem, those with certain medical illnesses, and those with idiosyncratic reactions to alcohol.

The majority of U.S. adults uses alcohol in amounts that could be defined as moderate (Klatsky et al. 1977a). These persons can be reassured that their drinking habit carries no known detrimental cardiovascular effects and may in fact place them in the most favorable risk category for overall cardiovascular disease incidence. With respect to alcohol use in relation to specific conditions, the following guidelines seem reasonable to the author.

1. Persons with chronic congestive heart failure or major arrhythmia problems should be extremely cautious about use of alcohol (no more than one drink per occasion).

2. Up to one or two drinks a day seems safe for hypertensive patients or persons at special risk of hypertension. Three or more drinks a day (35 ml or more of alcohol) probably increases the risk of hypertension.
3. Drinking before exercise is dangerous to patients with angina pectoris. Drinking before exercise is probably unwise for all persons.
4. Although a protective effect is not proved, the evidence is mounting that use of alcohol is associated with a slower rate of development of coronary atherosclerotic occlusion and a lower incidence of myocardial infarction. There is more epidemiologic evidence for this possible benefit at low to moderate levels of drinking (up to 30 ml of alcohol per day). At higher levels of drinking, the possible protection from coronary disease may be attenuated and, in any case, is outweighed by other cardiovascular risks.

## ***Research Needs and Problems***

### *Alcoholic Cardiomyopathy*

The case for the existence of alcoholic cardiomyopathy is strong but will remain circumstantial until specific diagnostic criteria are developed. A specific diagnostic tool would enable physicians to assess possible coexistence of alcoholic heart disease with other types of heart disorders, a situation likely to be clinically important. Unfortunately, success in finding diagnostic criteria does not seem imminent.

Epidemiologic and clinical studies are needed to determine the prevalence of heart toxicity indicators in association with regular use of various amounts and types of alcoholic beverages. Suitable indicators would be heart rhythm disturbances and evidence of decreased heart muscle pumping action at rest or with exercise. New noninvasive tools make such clinical research practicable.

Continuation of current research seems likely to further the understanding of basic biochemical mechanisms of alcohol cardiotoxicity. Animal experiments should be expanded to include study of the role of cofactors such as trace elements, deficiency states, and preceding viral myocardial injury. Such work might cast light upon the marked apparent variation in susceptibility of humans.

### *Hypertension*

Further epidemiologic studies should consider the question, "Does the association of substantial alcohol use with elevated blood pressures indicate an association with the *disease* hypertension?" Effects of high blood pressure on blood vessels and, ultimately, on the heart, kidneys, and brain are used as indicators of the disease. More work is clearly



needed on possible mechanisms for the blood pressure effects of chronic alcohol use. Possible effects on the volume-regulating system (the renin-angiotensin system) would be of great interest.

### *Coronary Artery Disease*

Further epidemiological work, with extremely careful control for cigarette smoking, is needed before the inverse relation of drinking to coronary events can be fully accepted. Important questions are: (1) What explains the possible differences in coronary disease between lifelong abstainers and former drinkers? (2) Why do problem drinkers apparently suffer more coronary events than other drinkers? Extensive work now underway on the possible link between alcohol use and atherosclerotic disease seems likely to continue. Work on other possible mechanisms for protection is needed, especially in the area of immediately protective effects against myocardial infarction and sudden death.

### *General Approach*

As the history of this subject clearly points out, generalizations and a simplistic approach must be avoided. The relation of alcohol to each cardiovascular condition should be studied as an independent subject. Since there is a strong possibility of a safe or even beneficial alcohol dose with respect to cardiovascular conditions, future research should place more emphasis on the health effects of low or moderate amounts of alcohol, with the clear definition of a safe dose a major goal.

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## Chapter 7



# **Alcohol, Cognitive Dysfunction, and Brain Damage**

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## **Abstract**

Both brain abnormalities and cognitive impairment are found in the majority of alcoholics in treatment programs after the acute withdrawal period (approximately 1 week) has passed. Evidence for altered brain structures in such alcoholics comes from computerized axial tomography (CAT) brain scan studies which suggest that the brains of alcoholics are atrophied or shrunk. Evidence for altered brain functioning comes from electrophysiological and cerebral blood flow studies.

Cognitive impairment in alcoholics also has been widely reported. While average or higher in verbal intelligence, both male and female alcoholics have abilities, the same abilities which are deleteriously affected by age and other types of brain dysfunction. Surprisingly, there are some indications of mild deficits in the same abilities in heavy social drinkers. This suggests a continuum of effects of drinking beverage alcohol ranging from no impairment in light and moderate social drinkers through occasional deficits in heavy drinkers to mild, moderate, and sometimes severe impairment in alcoholics.

The effects seem most parsimoniously attributed to a mild diffuse generalized brain dysfunction. Age is an important factor; older alcoholics manifest more impairment than younger alcoholics. In some respects alcoholics manifest characteristics of premature aging, but they differ from the elderly in other aspects of functioning.

Reversibility of brain and cognitive dysfunction in alcoholics has been a recent focus of attention. Partial reversibility of the altered brain structure, as measured by CAT scans after several months of abstinence, has been suggested by investigators, but the findings are controversial. A number of studies have reported improved cognitive functioning in abstinent alcoholics over time. However, even after 1 year of abstinence, alcoholics continue to manifest deficits in some areas, particularly on less practiced problem-solving and nonverbal abstracting tasks. Age may also be a critical variable in reversibility; older alcoholics may not recover to the same extent as younger alcoholics. An expanded study of reversibility of brain and cognitive



deficits in alcoholics is of critical importance for the thorough understanding and treatment of alcoholism.

## ***Introduction***

Does prolonged, repetitive overindulgence in alcoholic beverages affect the brain? The answer is clearly "yes," but a host of additional questions remain. Which brain structures are affected? Which mental (cognitive) abilities are impaired and to what degree? Are the effects different in males and females? Are immoderate social drinkers likely to have deficits similar to alcoholics? Does alcohol prematurely age the brain? Do cognitive deficits predict treatment outcome? Does the brain recover with abstinence? Do cognitive abilities recover? Are there different recovery rates for different mental processes? The current answers to these and other relevant questions constitute the body of this paper.

The evidence for the deleterious effects of alcoholism on the human brain comes from a variety of sources. First, there is biomedical evidence of altered brain structures and functions from autopsies, pneumoencephalograms (brain X-rays) and computer-assisted tomography scans (CT scans), cerebral blood flow procedures, electroencephalogram measurements (brain waves) and changes in event-related electrical potentials (brain reactivity), and biochemical, endocrinological, and psychopharmacological studies. A second line of evidence is based on the presence of cognitive and perceptual deficits in alcoholics on certain neuropsychological tests. These deficits are similar to those in patients with brain damage unrelated to alcohol. Finally, there are the well-described organic brain syndromes associated with alcoholism.

The effects of alcohol on the brain have been typically classified into two major categories of brain disease: acute brain syndromes and chronic brain syndromes. The acute brain syndromes vary from mild states of intoxication like those seen at any cocktail party to the potentially lethal withdrawal syndrome. In acute alcohol intoxication, memory, judgment, thinking, emotionality, psychomotor speed, and motor control are disturbed. These states are familiar to most of us through personal experience or daily observation. On the other hand, the withdrawal syndrome occurs within hours of stopping or reducing excessive drinking, lasts up to a week,<sup>1</sup> and is characterized by coarse tremors and other symptoms such as nausea, vomiting, malaise or

<sup>1</sup> There is evidence that the withdrawal syndrome may be present subclinically (no obvious clinical signs) for periods considerably longer than 1 week. Begleiter and Porjesz (1979), using the event-related potential technique, have described the persistence of a "subacute withdrawal syndrome" following chronic alcohol ingestion in both animals and humans, lasting for several weeks to a month. Thus, there may be two processes that affect behavioral studies of detoxified alcoholics: (a) the specific effects of alcohol withdrawal on the central nervous system, and (b) the possible long-term changes in the

weakness, rapid heartbeat, sweating, anxiety, and depression. Delirium or hallucinations may also be present. The disorder is usually reversible. We shall not discuss either of these acute alcohol-induced brain disorders further.

The chronic brain syndromes associated with alcoholism are typically slow and insidious, with major subtypes of dementia (general loss of cognitive abilities) and the amnestic syndrome (specific loss of recent memory and, to a lesser extent, remote memory). It has been estimated that approximately 10 percent of alcoholics presenting for treatment may fall into the "chronic brain syndrome" category (Parsons 1977). This condition usually is considered irreversible. A large number of alcoholics fall into the so-called intermediate stage of brain damage (Smith 1977) in which acute brain syndrome symptoms are absent and cognitive changes that may be present are not sufficient to diagnose chronic brain syndrome. The condition is considered reversible (Smith 1977) although, as we shall see, there are questions as to whether complete recovery occurs. This group of alcoholics constitutes the highest percentage of patients in alcohol treatment programs and is the primary concern of this report.

We discuss first the biomedical evidence for altered brain structure and function in alcoholics, focusing particularly on the computer-assisted tomography technique. Next we examine the behavioral evidence for cognitive dysfunction in alcoholics and identify the important variables that affect the findings. Recent contributions to a new area of research, the neuropsychological consequences of social drinking, are to be discussed. Then we evaluate current neuropsychological (brain-behavior) explanations for the behavioral deficits. We also consider the relationships between biomedical and behavioral measures and closely scrutinize the evidence for possible reversibility of biomedical and behavioral deficits. A summary of the current status of research and promising directions for future work concludes the paper.

## ***Altered Brain Structure and Function in Alcoholics***

Since the publication of Courville's (1955) post mortem studies of the brains of alcoholics, atrophy (loss of brain cells) has been considered one of the major consequences of alcoholism (Ron 1977; Wilkinson and Carlen 1981). Until recently, atrophy was measured in living patients by means of the pneumoencephalogram. In this procedure, spinal fluid is withdrawn and replaced with air or a gas; then X-rays are taken to reveal brain changes. The technique is invasive in that a spinal tap is performed, with some risk and discomfort. Several years ago Parsons (1977) summarized the results of a number of pneumoencephalographic studies of alcoholics in the world literature as follows:

structure and function of the central nervous system due to the neurotoxic effects of alcohol. Disentangling whether given behavioral deficits found in alcoholics who are examined 1 month after detoxification are due primarily to one or the other of these processes is not possible at this time.

There is little doubt of the consistency of findings. In any given sample of alcoholics the percent of individuals with atrophy will range from 50 percent to 100 percent. On the other hand, this percentage is obviously a function of selection criteria. . . in the unselective alcohol treatment program only about 50 percent to 60 percent will have such findings. (pp. 51-52)

Since that time computer-assisted tomography (CT scan) has become the preferred method for examining the structural integrity of the brain. The great advantage of this technique is that it is noninvasive and carries no risk or discomfort other than lying still for several minutes. Essentially, the technique consists of multiple X-ray exposures or scans of the brain from many different angles. The small differences in density of various structures are displayed on a cathode-ray screen in cross-sectional images or "slices." These images may be photographed with a Polaroid camera and judged clinically or measured quantitatively (Osborn 1979; Wedding and Gudeman 1980). The CT scan has been called the most sensitive, reliable, and valid noninvasive neuroradiodiagnostic procedure yet developed (Osborn 1979). It has been rapidly accepted throughout the world. What are the CT findings in alcoholism?

To understand the findings, it is necessary to briefly describe the two major types of CT scan indexes that are used for measuring atrophy: ventricular enlargement and sulcal width. The ventricles are cavities in the brain tissue, filled with cerebrospinal fluid. They are buried in the central part of the brain under the cortex (the brain's outer layer). When surrounding brain tissue atrophies or dies, the ventricles expand to fill up the space left by the vanished tissue. Measurements are made of such features as the widest point of the anterior horn (forward part) of the lateral ventricles, the width of the lateral ventricles in the region of the caudate (another brain structure), and the ratio of maximum width of ventricles to the width of the interior surface of the skull (the ventricle/brain ratio). When enlarged ventricles are found atrophy is inferred. The second major measurement is sulcal width. The sulci are the valleys in the external convolutions of the cortex, the outermost layer of the brain. When the sulcal widths become pronounced, atrophy is inferred. Such conditions are frequently found in senile patients.

The CT scan studies, summarized in table 1, have followed the progression characteristic of any new approach. The first reports established the potential of the line of inquiry but used small numbers of subjects and had methodological weaknesses; then gradual improvement on both dimensions occurred. The first two studies, for example, were performed on alcoholics who were referred for CT scans because of clinical indications. Naturally, a higher rate of abnormalities might be expected in this group than in alcoholics who are routinely given CT scans as part of a research program. In the first five studies a total of only 136 alcoholics were examined and no data on reliability of judgment of CT abnormalities were presented. However, in the next



three studies (Bergman et al. 1980*b*; Carlen and Wilkinson 1980; Ron et al. 1979) large numbers of alcoholics ( $N=326$ ) were examined on a routine research basis. Reliability estimates of CT indexes were reported and careful medical examinations were given to exclude other disorders. In these three studies the data are quite consistent for estimates of abnormal sulcal widening, 68 percent, 77 percent, and 62 percent, respectively. The ventricular enlargement data for the three studies are somewhat more variable, 77 percent, 60 percent, and 36 percent, respectively. The overall means of 69 percent for sulcal widening and 56 percent for ventricular enlargement are completely in accord with the percentage of abnormalities in the pneumoencephalographic studies summarized by Parsons (1977).

Returning to the results from the first five studies in table 1, it is evident that they are much more variable. The data from Epstein et al. (1977) and Cala et al. (1978) are presented in terms of "cerebral atrophy" apparently based on both ventricular and sulcal measurement. The data are consistent with the later studies (61.4 percent and 73 percent, respectively) but cannot be directly compared to them without a breakdown into the component CT indexes. It is probably no accident that the two studies with the lowest incidence of ventricular enlargement are the two with the youngest patients (Hill et al. 1979; Lee et al. 1979). The extensive data of Bergman et al. (1980*a, b*) in 195 normal subjects clearly indicate that both ventricular and sulcal widening are directly and linearly related to age. Ventricular widening is minimal in younger alcoholics but accelerates over the decades, while sulcal widening is seen in young alcoholics and is fairly constant over age in that group. The latter finding makes the report by Hill et al. (1979) of no patients with abnormal sulci almost inexplicable. Hill et al.'s alcoholics were quite impaired on neuropsychological testing, similar to the other alcoholic populations studied. But even Lee et al.'s (1979) younger group had a significant incidence of sulcal abnormalities! The most likely explanation lies in how "abnormal" sulci are defined. The criteria were not spelled out in Hill et al.'s 1979 report.

Table 1. Summary of Abnormal Computerized Tomography (CT) Findings in Alcoholics and Controls<sup>1</sup>

Authors (Year) Country	Number (N) Alcoholics (Controls)	Mean Age Alcoholics	Percentage Males	Duration Alcoholic (Years)	Percentage Abnormal			
					Ventricles	Sulci	Cerebral <sup>2</sup>	Cerebellar
Fox, Ramsey, Huckman, and Proske (1976) United States	12 (60)	46.4	58	5.0 +	75 (27)	17	-	-
Epstein, Pisani, and Fawcett (1977) United States	46	47.8	65	-	-	-	61.4	-
Cala, Jones, Mastaglia, and Wiley (1978) Australia	26	39.3	84	14.2	-	-	73.0	73
Hill, Reyes, Mikhael, and Ayre (1979) and Hill and Mikhael (1979) United States	15 (12)	34.0	100	14.3	7 (0)	0 (0)	-	-
Lee, Moller, Hardt, Haubeck, and Jensen (1979) Denmark	37	30.0	100	10.0	13	49	-	37
Ron, Acker, and Lishman (1979) England	100 (41)	43.5	100	17.3	71 <sup>4</sup>	68 (22)	-	-

Authors (Year) Country	Number (N) Alcoholics (Controls)	Mean Age Alcoholics	Percentage Males	Duration Alcoholic (Years)	Ventricles	Sulci	Cerebral <sup>2</sup>	Cerebellar
Carlen and Wilkinson (1980) Canada	96 (146)	45.0	88	10.0+	60 <sup>1</sup>	77 <sup>1</sup>	-	-
Bergman, Borg, Hindmarsh, Idestrom, and Mutzell (1980a, b) Sweden	130 (195)	44.2	100	11.0+	36 (11)	62 (16)	-	35 (5)
Bergman, Borg, Hindmarsh, Idestrom, and Mutzell (1980a) Sweden	18 <sup>3</sup> (180)	-	100	-	36 (11)	40 (14)	-	0 (5)

<sup>1</sup> Data in parentheses is for controls; in almost all studies where controls are used they are equated in age with alcoholics.

<sup>2</sup> Cerebral refers to ventricular and/or sulci widening without reporting the incidence of the two separate components.

<sup>3</sup> Excessive social drinkers from normative study.

<sup>4</sup> Percentage of alcoholics 1 standard deviation greater than controls.



Two additional points can be made. First, the number of female alcoholics on whom we have CT data is very small. Only the study by Epstein et al. (1977) analyzes these data. Women alcoholics appear to have the same incidence of atrophy as men but obviously more data are needed. Second, although the effects of heavy social drinking on the brain are just beginning to be explored, the initial findings are intriguing. The last entry in table 1 shows that 18 excessive social drinkers from a random sample of 200 control patients had definite cortical sulcal widening (40 percent), widened third ventricles (36 percent), and elevated ventricle/brain ratios. The comparable values for the remainder of the controls were 14 percent, 11 percent, and 10 percent!

### *Cerebral Blood Flow Studies*

The CT evidence for altered brain structures in alcoholism is convincing, but what about brain functioning? There is consistent evidence for altered brain functioning in alcoholics. Two areas of research seem particularly important.

In the early 1960s, Lassen and associates (1978) developed a method for measuring blood flow in various parts of the brain. Their approach was based on the fact that blood flow through the tissues of the body varies with the degree of functional activity and level of metabolism in those tissues. Since brain tissue needs energy to conduct its work, the amount of blood flow measured throughout the brain might give valuable clues on the functional (working) integrity of its various parts. The method Lassen et al. developed was to inject a small and relatively harmless volume of a radioactive gas (xenon 133) dissolved in a sterile saline solution into an artery to the brain. The arrival and presence of the radioactive gas is followed by a camera consisting of 254 detectors monitoring many brain regions. A more recent method uses a gas inhalation technique and 32 detectors (Risberg 1980). The information is fed to a computer, which displays the data in a color-coded form on a color television monitor. Investigating the blood flow in a variety of patients under a variety of stimulus conditions, Lassen et al. (1978) and Risberg (1980) demonstrated an impressive potential for their technique, especially in the study of dementia.

Given the presence of cognitive dysfunction (Hagberg and Ingvar 1976) and the incipient dementia in many alcoholics, would cerebral blood flow be disturbed in alcoholics, and if so, would these disturbances resemble those in patients with clear-cut dementia? To answer these questions, Berglund and Ingvar (1976) compared resting cerebral blood flow levels of 53 alcoholics (mean age 45) to groups of preseniles (individuals with dementia but younger than "senile" patients), schizophrenics, and healthy controls. They found significantly reduced blood flow values in alcoholics for both grey matter (brain cells) and white matter (brain nerves). Unlike healthy controls and schizophrenics, the lower blood flow was linearly related to increasing age: the older the

alcoholic, the lower the cerebral blood flow. Alcoholics over 45 had significantly greater reduction in flow to the lower frontal and anterior temporal areas than younger alcoholics.

In the next study (Berglund, Gustafson, Hagberg, Ingvar, Nilsson, Risberg, and Sonesson 1977), 15 chronic alcoholics and 15 presenile patients were matched on mean hemisphere resting blood flow values and were found to have no differences in their regional resting blood flow (frontal, temporal, etc.). However, the alcoholics performed significantly better than the presenile patients in tests of cognitive function. The authors speculated that the alcoholics may be able to better activate their brains when faced with tasks than the preseniles, and cited some previous research with alcoholics to support the hypothesis. It is clear that cerebral blood studies may give us new insight into the functioning brain (Risberg 1980). We can anticipate future in-depth studies of alcoholics with this technique.

### *Event-Related Potentials*

Another major line of research on brain functioning is the event-related potential (ERP). Records of electrophysiological activity of the brain (brain waves) are made during repetitions of certain stimuli. The records are then averaged by a computer to produce a typical stimulus-induced undulating response wave. The ERP has been found to be a remarkably sensitive measure of central nervous system disorders (Beck et al. 1975). Certain components of the wave have been shown to be related to attentional and evaluative processes in normal individuals (Porjesz and Begleiter 1979).

Beck and colleagues (1978) compared the responses of young normals, young alcoholics, and elderly normals to visual stimuli. Young alcoholics and elderly normals had significantly longer latencies and lower amplitudes of late components of the response wave than young controls. The authors suggested that the similar nature of the findings for young alcoholics and the elderly supports the notion of "premature aging" in alcoholics. Porjesz and Begleiter (1979) and Pfefferbaum and associates (1979) report results distinguishing alcoholics from age-matched controls; latency and amplitudes of late components are increased in the alcoholics. As these measures are also abnormal in dementia, Pfefferbaum et al. conclude that they reflect mild dementia in the alcoholics. This cognitive disturbance is found despite the fact that attentional and sensory filtering processes seem intact as judged from the lack of differences in early components of the wave. Porjesz and Begleiter (1979) report that visual ERPs in their alcoholics did not manifest the usual right hemisphere superiority seen in their controls and, further, that the greatest differences in reduced amplitude in the alcoholics were found over the right frontal electrode placement.

Clearly the cerebral blood flow and ERP studies point to altered brain functioning in alcoholics who have been detoxified for several weeks

and are past the withdrawal phase. The systematic study of alcoholics with both of these techniques is in its infancy.

### ***Behavioral Deficits—Cognitive Dysfunction***

Before discussing cognitive dysfunction in alcoholics it will be well to remind the reader that we are focusing on the "intermediate stage" chronic alcoholic. Very few of the studies cited here initiated psychological examination of the alcoholic until after the acute withdrawal period (usually a minimum of 1 week). Most of the studies cited do not include the approximate 10 percent of alcoholics who have clinically diagnosed brain syndromes.

It is also important to point out that mental functioning, i.e., cognitive behavior, is quite directly affected by sociocultural factors. These factors have less effect on biomedical measures of the brain's structure and functioning. For example, it is unlikely that CT scan measures of atrophy are directly affected by education, although the latter's importance in determining performance on problem-solving abstracting tasks is widely recognized. Age, education, sex, and degree of psychiatric disturbance (e.g., depression) are among the most important variables that must either be controlled or their effect measured (Parsons and Prigatano 1978). For alcoholics there are a number of additional factors. Duration of heavy drinking is important. On some cognitive tasks deficits are seen only in the long-term (over 10 years of heavy drinking) alcoholic (Parsons 1977). Duration of abstinence before testing is also important. Some investigators have reported that the longer the period of abstinence, the better the performance of alcoholics on certain tasks (Goldman in press). A number of medically related variables can influence performance. Liver disease is common in alcoholics and can lead to brain changes and cognitive deficits independent of alcohol (Smith and Smith 1977). Poor nutrition could affect performance in a variety of ways besides direct effects on the brain; e.g., a malnourished individual may be less persistent in problem-solving or less efficient as tasks increase in difficulty. Head trauma is common in alcoholics and could lead to brain effects that are mistakenly attributed to alcohol. Patients with other chronic medical conditions that may affect the brain such as diabetes, obstructive pulmonary disease, hypertension, and endocrine disorders all must be carefully screened out if the nature of alcoholism effects on the brain is to be understood. Fortunately, investigators in this complex field have become increasingly sophisticated. In most studies, explicit control or allowance for most of the variables described above has been made. In our coverage below we note omission of important control variables, but otherwise it can be assumed that the study is sound.

Let us now turn to studies of cognitive dysfunction in alcoholics. Intelligence is one of the most important factors in all of human



behavior and therefore will be considered first. Next we review evidence for other impaired mental abilities as measured by neuropsychological tests in alcoholics and social drinkers.

### *Intelligence: The Wechsler Adult Intelligence Scale*

Our best measure of adult intelligence is the Wechsler Adult Intelligence Scale (WAIS). In addition to being an overall measure of general intelligence it provides two subtypes of intelligence, a 'Verbal' Scale IQ and a "Performance" Scale IQ. The former consists of tests that are highly language-related, e.g., Vocabulary, General Information, Similarities (verbal abstracting), Comprehension (verbal understanding), Digit Span (immediate recall of digits), and Arithmetic (verbal problems). The Performance Scale is comprised of perceptual-motor and problem-solving tasks including Digit Symbol (a timed coding of symbols), Block Design (reproduction of visual-spatial patterns), Picture Completion (identification of essential missing elements in a picture), Object Assembly (completion of jigsaw-like puzzles), and Picture Arrangement (ordering of cartoon-like pictures to tell a story). The Performance Scales require no verbal response, only some type of manipulation of objects. The differences between these two types of intelligence have been clearly established over the last 30 years.

Parsons and Farr (1981) recently reviewed cross-national studies of intelligence and neuropsychological functioning in alcoholics. Many of these studies were done on Veterans Administration Hospital patients, but State and private clinics also are represented. Verbal IQs and Performance IQs were noted in 14 of these studies. The mean Verbal IQ was 108.7 and the mean Performance IQ was 104.7. Both values are in the average range of intelligence (90-110). These results agree with many previous conclusions (Goodwin and Hill 1975; Parsons 1977). Alcoholics in treatment programs in a variety of institutions are of average intelligence, and in fact are slightly above the mean IQ of 100.

For eight of these studies we were able to calculate the percentage in which the alcoholics were significantly lower than their controls on each of the individual subtests comprising the Verbal and Performance Scales. For subtests on the Verbal Scale, none of the percentages were over 50; for the Performance Scale, percentages on four of the five subtests were above 70 percent. On Block Design (visual-spatial pattern reproduction), alcoholics were significantly lower than controls in all eight (100 percent); on Object Assembly (jigsaw-like puzzles), 86 percent; on Digit Symbol (coding speed), 75 percent. Thus, despite the closeness in IQs (in these eight studies, Verbal IQ=108.9; Performance IQ=105.6), there were significant differences on several individual subtests of the Performance Scale. These subtests are also more sensitive to the effects of brain damage and aging than are Verbal Scale subtests, a point to which we return later.

In general, verbal abilities as measured by our best adult intelligence test appear to be intact in alcoholics, but visual-spatial constructional

abilities and perceptual-motor coding speed are mildly impaired when compared to controls' performance.

*Neuropsychological Functioning: Halstead-Reitan Battery and Luria Nebraska Battery*

Neuropsychological tests have been developed specifically for detecting brain dysfunction. The most widely used neuropsychological battery of tests is the Halstead-Reitan Battery (HRB). The validity of the HRB in detecting impairment in brain damage has been established in scores of studies (Boll 1978). It provides measures of a variety of cognitive and perceptual-motor functions: nonverbal abstracting behavior (Category Test); tactual-spatial speed and problem-solving behavior (Tactual Performance Test-Time, TPT-Time); incidental memory for tactually perceived shapes (TPT-Memory) and their location in space (TPT-Location); auditory rhythm pattern detection (Rhythm Test); speech discrimination (Speech-Sounds Perception Test); and motor speed (Finger-Tapping Test). Each test is scored in the normal or abnormal range according to cutoff points that discriminate brain-damaged and non-brain-damaged patients. The ratio of tests in the brain-damaged range to total number of tests constitutes an Impairment Index with a range of 0 to 1.0. This Index has been shown repeatedly to be the best single overall measure in the Battery for identifying impairment.

In the Parsons and Farr review (1981), 13 of 15 studies (87 percent) found the Impairment Index to be significantly higher in alcoholics than in comparable nonalcoholic controls. However, the overall mean Impairment Index for alcoholics was 0.49, slightly below the cutoff point for impairment (0.50 and above). In 7 of 13 studies (54 percent) the Index for the alcoholics was in the "impaired" range. The six studies in which the Impairment Index was under 0.50 were comprised of younger or better educated subjects. As noted earlier, age and education are critical variables when cognitive and perceptual-motor functions are being tested. Nevertheless, when these variables are controlled, alcoholics perform significantly more poorly than their comparison groups, and their average impairment is in the borderline to moderate range.

Analysis of the pattern of differences between alcoholics and controls in component tests of the HRB reveals several interesting facts. Nonverbal abstracting ability as measured by the Category Test was significantly lower in alcoholics in 87 percent of 15 studies. Tactual-spatial problem-solving speed (TPT-Time) was impaired in 80 percent, and location of tactual shapes in 62 percent. Perceptual-motor speed (Trail-Making Test-B) was poorer in 73 percent of the studies. Alcoholics had deficits on the Speech-Sounds Perception in 50 percent of the studies but performance on the other HRB tests (Rhythm, Finger-Tapping, TPT-Memory) was only occasionally (25 percent or less) impaired.

Considering the results with the WAIS and HRB, we find alcoholics performing relatively poorly on visual-spatial (Block Design and Object Assembly) and tactual-spatial (TPT-Time and TPT-Location) constructional tasks; nonverbal abstraction (Category Test) and perceptual-motor speed (Trails B and Digit Symbol). Except for the Object Assembly Test, the remaining six tests are the components of the Brain-Age-Quotient (BAQ) developed by Reitan (1973). These tests systematically decline with age and are more sensitive to any type of brain dysfunction than are other HRB and WAIS tests. Schau and O'Leary (1977) specifically examined male alcoholics and controls for deficient BAQs and found alcoholics were significantly lower. Our review of other neuropsychological studies certainly supports their findings.

A new standardized neuropsychological test battery based on the work of the renowned Russian neuropsychologist, A. R. Luria, has been developed by Golden and his colleagues at the Nebraska Psychiatric Institute (Golden 1981; Golden et al. 1978; Purisch et al. 1978). This battery, the Luria Nebraska Neuropsychological Battery (LNNB), has been shown to be a reliable and valid indicator of brain dysfunction (Golden 1981). The psychological functions measured by the LNNB are more specific and better defined than on the HRB as indicated by the following 11 scales: Motor Function, Rhythm and Pitch, Tactual and Kinesthetic Functions, Visual Functions, Receptive Language, Expressive Language, Writing, Reading, Arithmetic, Memory, and Intelligence. Profiles of performance are plotted using standardized scores, so patterns of deficit performance for different types of brain dysfunction are possible.

The LNNB has been administered to alcoholics in two separate studies. The first study (Chmielewski and Golden 1980) compared 40 male middle-aged hospitalized alcoholics with nonalcoholic hospital patients. On 5 of the 11 scales (Visual, Receptive Language, Arithmetic, Intelligence), alcoholics were significantly poorer than controls. They also differed on the Pathognomic Scale, a derived scale comprised of the most brain dysfunction discriminating items from all the scales. The authors concluded that alcoholics have a diffuse brain dysfunction. In our laboratories, de'Obaldia, Parsons, and Leber (in press) compared 30 male middle-aged VA alcoholics to 15 healthy community control males. The alcoholics were significantly poorer on every scale of the LNNB except Reading. Again the authors concluded that the alcoholics suffered from a mild diffuse brain dysfunction.

### Female Alcoholics

There is only one published study of neuropsychological functioning in female alcoholics using the HRB or LNNB. Silberstein and Parsons (1981) compared 25 female middle-aged alcoholics with 25 community controls on a number of neuropsychological tests including five from the HRB and several WAIS subtests. Significant differences were found between groups on many of the HRB and WAIS subtests, especially



those comprising the BAQ, confirming findings with males (Schau and O'Leary 1977). In a second and larger study we have factor-analyzed a number of neuropsychological test results in female alcoholics and controls. (Factor analysis is a statistical technique that reduces a large number of intercorrelated variables to a smaller set of factors based on the underlying pattern of relationships in the data.) Seventy-three alcoholics and 37 controls were tested in the first study; 35 alcoholics and 35 controls comprised the cross-validation study. Factor structures (interrelatedness of the tests) in the two studies were similar for both alcoholics and controls. Therefore, the alcoholics and controls were combined and factor-analyzed separately for Study 1 and Study 2. In both studies our 17 test scores were reduced to four factors. Factor 1 consisted of perceptual-spatial, nonverbal abstracting, problem-solving tasks. Factor 2 involved verbal and language tests. These two factors were the most important in predicting the variation among subjects' scores. Factor 3 was relatively specific for factual memory, and Factor 4 was visuo-motor scores were calculated for each factor. Overall statistical analysis across all tests indicated that the alcoholics performed more poorly than controls in both studies ( $P < .01$ ). However, the differences between groups were centered in Factor 1, the only factor to give rise to highly significant group differences ( $p < .001$ ) in both studies. By way of comparison, in both studies the alcoholics were indistinguishable from the controls in Factor 2 (Verbal-Language) scores. It is also interesting that all of the brain-sensitive BAQ Tests except TPT-Location are very highly represented on Factor 1 and have no significant contribution to Factor 2. Conversely, the Verbal Tests which define Factor 2 have inconsequential representation on Factor 1.

It is very clear that female alcoholics exhibit the same pattern of less efficient functioning on neuropsychological tests as their male counterparts, namely, relatively intact verbal functions and poorer perceptual-spatial, nonverbal abstracting, and problem-solving abilities.

In summary, alcoholics in treatment programs in different countries and throughout the United States typically range from average to slightly above average on both verbal and performance intelligence. However, certain visual-spatial and perceptual-motor subtests of the WAIS Performance Scale are significantly lower in alcoholics compared to controls. In the neuropsychological studies with the HRB there is consistent evidence for mild impairment of adaptive abilities. Specific patterns of deficit performance occur on tests that make up the Brain-Age Quotient. These tests have been shown to be quite sensitive to brain dysfunction and to aging. A general decrement in neuropsychological functioning in alcoholics is indicated on the new Luria Nebraska Neuropsychological Battery. Finally, males and females manifest the same pattern of neuropsychological deficit. It is evident that these Intermediate Stage alcoholics who present to treatment programs (and do not have clinically diagnosable brain disorders) have a mild but significant neuropsychological impairment, especially on tasks involving

problem-solving, nonverbal abstracting, and perceptual-spatial-motor abilities.

### *Neuropsychological Functioning in Social Drinkers*

The boundary between excessive social drinking and alcoholism is not distinct. A "heavy" social drinker may drink as much alcohol as a diagnosed alcoholic for at least a while, and there are persons in alcoholic treatment programs who insist they are merely heavy social drinkers. It is reasonable to suppose that as the quantity, frequency, and duration of alcohol intake increase in the progression to alcoholism, mild forms of the symptoms should appear as harbingers of more definite patterns of deficit to come later. This important issue has received relatively little attention. Parker and Noble (1977) reported using a sophisticated sampling technique to assemble 102 men who were gainfully employed at a fairly high occupation level. They were given alcohol usage questionnaires and a neuropsychological test battery. Neither frequency of drinking nor lifetime consumption of alcohol predicted test performance. However, the average amount of alcohol drunk at any one occasion was significantly and inversely related to performance on the Shipley Institute of Living Vocabulary and Abstracting scores, the Halstead Category Test, and the Wisconsin Card Sorting Test (WCST). (The latter is a test of ability to form concepts and to shift set.) Parsons and his colleagues (Jenkins and Parsons 1980; Klisz and Parsons 1979) have repeatedly demonstrated impaired performance by alcoholics on the WCST. In a subsequent article Parker and Noble (1980) found that the correlations between amount of alcohol drunk per occasion and performance on the WCST were significantly higher in the 49 social drinkers above age 45 than in the 53 social drinkers below that age. Thus, age and amount of alcohol drunk interact; the older the social drinker and the more he drank per occasion, the poorer the performance. This relationship was not present in the young group.

The effects of history of social drinking on memory in female alcoholics were examined by Jones and Jones (1980). While the primary focus of their investigation was on the effects of an acute dose of alcohol on memory for word lists, they also analyzed their data for differences between light and moderate social drinkers (defined by amount drunk the previous month) on baseline memory measures (i.e., before being given alcohol or placebo). Moderate social drinkers had significantly poorer memory scores than light social drinkers. The effects of a single acute dose of alcohol were greater in the moderate social drinkers than the light social drinkers. Again, both the quantity of alcohol consumed and the age of a social drinker were important factors.

The third study of nonalcoholic social drinkers is that of Bergman et al. (1980a). The 18 "excessive social drinkers" in that study are probably closer in their drinking behavior to alcoholics than are the

social drinkers of the previous studies. This was the group that had significantly more abnormal CT measures (table 1) than the remainder of the normal group. They also had significantly lower scores on the Block Design Test, the Halstead-Rhythm Test, the Impairment Index, and the Memory-for-Design Test. The latter is a measure of visual-spatial memory on which male alcoholics have shown deficits (Leber et al. 1981). Finally, the "heavy drinkers" reported by Cala et al. (1978) had significantly lower WAIS subtest scores on Digit Symbol, Block Design, and Object Assembly in comparison to their scores on Vocabulary and Picture Completion. This pattern is the same as the WAIS findings in diagnosed alcoholics.

There seems to be some validity to the notion of a continuum of alcohol effects on cognitive functioning. The continuum ranges from no impairment in light social drinkers, occasional inefficiencies in moderate drinkers, mild deficits in heavy social drinkers, mild to moderate impairment in Intermediate Stage alcoholics, to the moderate-severe impairment in the dementias and the Wernicke-Korsakoff syndrome. The latter part of the continuum (from alcoholism to Korsakoff's syndrome) has been emphasized by Butters and his colleagues (Ryan et al. 1979) and is covered in detail in the present volume. It should be emphasized, however, that studies of social drinkers are just beginning to appear. Undoubtedly in the next decade we will gain much more information in this important area.

### ***Neuropsychological Functioning—Theories***

There is no question that biomedical and behavioral evidence point to a mild brain dysfunctional state in the Intermediate Stage alcoholic. Which aspects of brain structure and function are affected most? Almost a decade ago Jones and Parsons (1971) offered three neuropsychological hypotheses to explain deficit behavior in alcoholics: a general, diffuse state of brain dysfunction; a predominantly frontal lobe dysfunction; and a predominantly right hemisphere dysfunction. The notion of a diffuse brain dysfunction in the Intermediate Stage alcoholic has been discounted (Parsons 1977) mainly because the deficits are selective; i.e., verbal language-related measures of intelligence appear to remain largely intact while the problem-solving, nonverbal, and perceptual-spatial abilities are decreased.

Tarter (1976) surveyed the behavioral evidence from human and animal studies and concluded that the most promising neuropsychological hypothesis was the "frontal-limbic-diencephalic" one. The hypothesis is attractive for two reasons. First, CT scan and pneumoencephalographic studies have repeatedly shown ventricular (both lateral and third ventricles) enlargement suggestive of atrophy in alcoholics. The cerebral region of the brain particularly around the third ventricle is the region through which frontal-limbic diencephalic connections traverse



(Tarter 1976). Atrophy in this region could give rise to disturbed frontal lobe functioning. Second, alcoholics show behavioral deficits in both experimental and life problem-solving situations that are similar to those found in patients with known frontal lobe dysfunction. While they may offer appropriate verbal solutions and explanations, their behavioral solutions leave something to be desired. It is as though they cannot carry out a plan successfully or work adaptively toward a goal. Such behaviors are also found in patients with known frontal lobe dysfunction from other causes.

The right hemisphere hypothesis was based on the similarity of performance patterns in alcoholics to patients with known right hemisphere damage, i.e., relatively intact verbal skills but impaired perceptual-spatial skills. Note that in this hypothesis we did not assume that the right hemisphere was damaged more than the left in alcoholics but that the functions of the right hemisphere were more vulnerable than the functions of the left to noxious influences like alcohol. The overlearned, continually rehearsed, verbal, analytic functions of the left hemisphere could be more resistive to the toxic alcohol effects than the nonverbal, perceptual-spatial, synthetic functions of the right hemisphere. Of course, all three hypotheses may hold; there may be a mild generalized-diffuse condition, in which the more vulnerable functions of the right hemisphere are most affected, accompanied by a central atrophy that results in disturbed frontal-limbic connections.

Unfortunately, there is no consistent evidence warranting the selection of one of these three hypotheses over the others. Let us first consider the generalized-diffuse hypothesis. While differences between intact verbal and impaired nonverbal abilities suggest that deficits are not generalized, this may be a function of the measures used. For example, several studies have found impaired verbal problem-solving performance in alcoholics (Bergman et al. 1980b; Gudeman et al. 1977; Guthrie and Elliot 1980). The two recent studies with the Luria Nebraska Neuropsychological Battery (Chmielewski and Golden 1980; de'Obaldia et al. in press) also support the mild general-diffuse hypothesis.

The frontal-limbic hypothesis remains attractive, especially with the evidence for reduced cerebral blood flow in the lower frontal regions (Berglund and Ingvar 1976), but anterior temporal blood flow was also reduced. The findings by Porjesz and Begleiter (1979) of reduced ERPs in the frontal region also support the frontal-limbic hypothesis, but ERPs were also reduced in the parietal areas. Behavioral deficits in tasks involving planning, problem-solving, set shifting, in alcoholics and frontal lobe patients but also can be found in generalized-diffuse disorders. Using the Luria Battery we found little indication of selective frontal-lobe dysfunctioning in alcoholics (de'Obaldia et al. in press).

The right hemisphere hypothesis is tantalizing in that occasional reports keep it alive and struggling. Cutting (1978) compared a number of brain-impaired groups on picture recognition and verbal learning tasks. The only groups with the same pattern of performance were the alcoholics and right temporal lobectomy patients. Miglioli et al. (1979)

readministered verbal and visual-spatial memory tests to middle-aged alcoholics and controls after 2 months: Verbal memory improved significantly but nonverbal memory showed no significant change. They interpret these data as supportive of the right hemisphere hypothesis. A similar experiment by Leber and colleagues (1981) led the authors to a similar conclusion. Another line of evidence comes from the studies of alcoholics' performance on the TPT-Time. Jenkins and Parsons (1979) and Fabian et al. (1981) have presented evidence that right-handed alcoholics' impairment on this test is due primarily to the left hand performance. As the left hand is under the direct control of the right hemisphere, the finding (in both males and females) suggest support for the right hemisphere hypothesis. However, an alternative explanation could be that a general, diffuse brain dysfunction might affect the less practiced hand differentially, i.e., it is not the perceptual-spatial functions of the right hemisphere that are disrupted but any behavior that is less firmly established or practiced. Finally, a number of investigations, including ours, using a variety of tasks, have raised questions on the tenability of the right hemisphere hypothesis, at least in its simplified form (Blackburn and Parsons 1980; L/berg 1980; Wilkinson and Carlen 1980).

Two other hypotheses deserve consideration. Tarter et al. (1977) suggested that at least some alcoholics, the so-called "primary" alcoholics, may have had a minimal brain damage syndrome (MBD) in their youth. Primary alcoholics are those who have histories of beginning drinking early and becoming alcoholic at a younger age than other alcoholics. They also have more extensive and intensive patterns of alcohol ingestion. Tarter et al. (1977) found that a group of primary alcoholics recalled more behavior or symptoms associated with MBD's being present before they were 12 years old than other alcoholics or psychiatric and control patients. If in fact they did have MBD, then in a substantial number of alcoholics the neuropsychological deficits may reflect a prealcoholic pattern of mild cognitive dysfunction. Obviously, this hypothesis needs thorough investigation.

The final hypothesis to be discussed is "premature aging." This hypothesis asserts that effects of alcoholism on the brain are similar to those found in aging. We have made a number of references to this hypothesis in preceding pages and comment again on it in the next section. For the present, based on our recent review of the concept (Leber and Parsons in press), we point out the decided similarities between the effects of aging and alcoholism in both the biomedical and behavioral-cognitive areas. However, there are also important differences. End-states such as ventricular and sulcal enlargement, impaired cognitive functioning on specific tests, and abnormal brain evoked potentials can result from vastly different processes. The possible reversibility of alcohol effects, currently the focus of many investigations, also challenges the premature aging concept. Only future research can establish the extent of the identity between alcoholism and aging effects on specific processes and specific end-states.

Meanwhile, the premature aging hypothesis remains an open and intriguing question.

### ***Relationship Between CT Scan Measures and Neuropsychological Test Performance***

We have cited ample evidence that alcoholics have abnormal CT indexes and lowered neuropsychological test performance. We have also noted that the neuropsychological theories of which brain functions are impaired are not conclusive. Consideration of the relationship between the findings of the two methods of measurement in the same subjects may be informative. The results of such studies are summarized in table 2. The findings range from no relationship to modest but significant correlations between CT indexes and cognitive measures. Fox et al. (1976) found no behavioral impairment, but they used a clinical mental status examination restricted to orientation and memory. Epstein et al. (1977) also did a retrospective mental status examination and found no significant relationship with CT measures, although 63 percent of their patients with atrophy had abnormal mental status exams compared to 37 percent of patients without atrophy. Cala et al. (1978) found significant correlations between degree of cerebral atrophy and three WAIS subtests—Digit Symbol, Block Design, and Object Assembly—but it is unclear whether these age-sensitive tests were corrected for age.

Hill and Mikhael (1979) and Hill et al. (1979) related the HRB and Shipley Institute of Living Scale to CT measures. According to the Impairment Index, 75 percent of the alcoholics were impaired compared to 0 percent of the controls. CT measures correlated minimally with test performance, but only 1 of their 15 alcoholics had an abnormal V/B ratio. Lee et al. (1979), using selected WAIS subtests, color-form sorting, and verbal and nonverbal learning tests, found that 59 percent of their alcoholics were intellectually impaired. However, no significant correlations between the two measures were found. Ron et al. (1979) found their 100 alcoholics were significantly poorer than controls on a



Table 2. Summary of Relationships Between CT Scan Findings and Behavioral Measures of Cognitive Dysfunction in Alcoholics<sup>1</sup>

Authors (year)	Behavioral Measures and Impairment	Relationships
Fox et al. (1976)	Clinical Mental Status Exam for Orientation and Memory Impairment: none	None: "normal" mental status
Epstein et al. (1977)	Clinical Mental Status Exam rated as impaired or nonimpaired Impairment: 57 percent	63 percent alcoholics with CT cerebral atrophy impaired 37 percent patients without CT atrophy impaired $\chi^2 = 1.10, P = N.S.$
Cala et al. (1978)	WAIS, Wechsler Memory Scale Impairment: alcoholics significantly poorer on Digit Symbol, Block Design, and Object Assembly; Memory appropriate to IQ	Significant correlations between degree of cerebral atrophy and Digit Symbol, Block Design, and Object Assembly but none with Vocabulary or total IQ
Hill and Mikhael (1979)	HRB-Selected tests, Shipley	CT measure V/B correlated significantly with category ( $r = .27$ ) but not TPT or impairment index
Hill et al. (1979)	Impairment: using Impairment Index, 75 percent alcoholics; 0 percent controls	
Lee et al. (1979)	WAIS-Selected Subtests, Verbal and Nonverbal learning, Goldstein Color-Form Impairment: 59 percent of alcoholics had signs of intellectual impairment	No significant correlations between psychometric tests and CT measures
Ron et al. (1979)	Reading Tests, WAIS-Selected Subtests, WCST, Verbal and Nonverbal Memory Impairment: alcoholics significantly poorer on all tests	Preliminary investigation failed to disclose any patterns of deficit associated with CT measures

## Relationships

## Impairment: alcoholics impaired on Memory-for-Designs

This report replaces Bergman et al. (1980a,b) from table 1. The same sample of alcoholics are used but the correlations between CT and neuropsychological tests are given in the 1979 paper

reading test, WAIS selected subtests, the WCST, and memory tests. However, their "preliminary investigation" of the relationship between the behavioral and CT measures was barren. Perhaps more detailed analyses will prove fruitful. The results of the studies reviewed so far have been disappointing. However, with the exception of Ron et al. (1979), these studies have many methodological problems that make them less than definitive.

The two most sophisticated studies, which also have large sample size, give us more hope. Wilkinson and Carlen (1980) used the WAIS, the Wechsler Memory Scale, and the HRB in their examination of 25 amnesic (Korsakoff) patients and 68 "other" alcoholics. About half of the latter were clinically diagnosed as impaired on the basis of neurological examination; the remaining half were similar to the patients we call "Intermediate Stage." The results, summarized in table 2, are complex. In the "other" group, there were many significant correlations between CT measures and neuropsychological tests (76 of 102). When age was partialled out, this number dropped to a paltry 2. The authors attribute this shrinkage to the accelerating effects of age on both test performance and CT measures in the "other" alcoholics. In contrast, age in the amnesic group was unrelated to CT indexes and had minimal relationships with the behavioral measures. The authors concluded that their data suggest at least two groups of alcoholics with functionally distinct brain syndromes. The first group ("other") comprises about 73 percent of their total sample. These patients have definite evidence of ventricular and sulcal widening as well as cognitive impairment. The most significant correlations occur between CT indexes and measures of problem-solving and new learning; however, partialing out age in this group eliminates these relationships. Wilkinson and Carlen (1980) suggest that these data support the hypothesis of premature aging in this group. In contrast, the second group (amnesics) is distinguished not only by poor memory but by high correlation between CT measures and the encoding and retrieving of verbal material. Age is not a significant factor in either CT or behavioral measures in this group.

The final results considered here are from a study at the Karolinska Institute in Stockholm (Bergman et al. 1979, 1980a, b), the largest CT study of both alcoholics ( $N=130$ ) and controls ( $N=195$ ) ever reported. In their 1979 report, Bergman et al. noted that approximately half of their 130 alcoholics had an HRB Impairment Index in the impaired



range, including 25 percent of their 20- to 29-year-old group. As in the Wilkinson and Carlen (1979) study, numerous significant although modest correlations (30 out of 45 comparisons) were present only to be reduced (9 of 45) by partialing out age. With age out, the Impairment Index remained correlated with sulcal widening ( $r = +.22$   $p < .05$ ) but not with ventricular measures. On the other hand, ventricular widening remained more highly correlated with general intelligence, learning, and memory abilities than sulcal measures. Finally, the authors report an interesting comparison of the correlations between the third ventricle and cortical (sulcal) changes as a function of age: in the 20-29 age group these correlations were moderately strong (around 0.40); they were insignificant in the 50-65 age group (around 0.10). Similar relationships were found for anterior horn index vs. sulcal changes. These findings imply that the older the alcoholic is, the more likely that cortical (sulcal) and ventricular atrophy are relatively independent processes. This suggests an important point: correlations between CT measures and behavioral measures might differ within age ranges (e.g., before and after 40).

In their study of 195 normal men, Bergman et al. (1980a) report correlations between 3 CT measures and 15 behavioral tests. Of 45 possible correlations, 32 were significant; partialing out age resulted in only 2 remaining significant. With age *not* partialled out, the alcoholic and control groups had 21 significant correlations in common. These consistent relationships were fairly evenly dispersed over the three CT measures. Bergman et al. (1980b) compared the ability of CT measures and neuropsychological tests to discriminate alcoholics from normals. Using a discriminant function analysis, 77 percent of the two groups were classified correctly by the CT scan and 74 percent by the behavioral measures. Thus, the two techniques gave rise to the same degree of classification despite the relatively low correlations between the measures. In summarizing their studies, Bergman et al. (1980b) concluded that two different patterns of neuropsychological deficits were observed. Deficits in abstracting ability were observed fairly uniformly throughout the age ranges, apparently paralleling the age-dependent sulcal (cortical) changes. On the other hand, short-term visual memory shows faster impairment with increasing age, similar to the ventricular (central) age relationships.

In a recent meeting, Golden (1981) reported correlations between the Luria Nebraska Battery Scales and the ratio of ventricle area to brain area (V/B ratio) in 25 alcoholics (data not included in table 2). CT planimetric measurement by three independent observers showed high reliability. Six of the Luria Scales (Motor, Visual, Expressive Speech, Memory, Intelligence, and Pathognomic) correlated with the V/B ratio after age and education were partialled out. The higher the ratio, the poorer the cognitive performance. If these results can be extended and confirmed, they will make an important contribution to this rapidly growing area of research.

In summary, it is safe to say that the relationships between CT indexes and cognitive dysfunction are modest at best. There are good reasons why this is not a discouraging conclusion. First, the trend of the research has been toward increasingly precise and sophisticated CT measures. As this has occurred, more significant relationships have emerged. Second, different cognitive deficits may accompany different CT measures of brain change. For example, sulcal (cortical) changes may correlate more highly with abstracting and problem-solving behavior while ventricular enlargement may relate more to learning and memory. Therefore, increasing specification of the relationships between CT measures and behavior measures may lead to clearer results. Third, the relationships between CT measures and behavior may differ as a function of age so that systematic study of the relationships over decades, or at least comparison of individuals over and under 40 years of age, may yield quite different findings. Fourth, it must be remembered that the CT scan indexes reflect structural changes. When we become able to measure altered brain *functioning* in conjunction with the altered *structures*, we should expect to see major increments in our knowledge of the relationships between brain and behavior.

## ***Reversibility***

The question of reversibility of dysfunction in alcoholics is clearly of great practical and scientific importance. The degree to which structural changes in the brains of chronic alcoholics are reversible affects our conceptualization of both the effects of alcohol and the reorganizational capacity of the brain. At the behavioral level, the degree to which cognitive recovery may occur in alcoholics has implications for many areas of their lives, particularly employment and education, and might also have an impact on their ability to participate in therapeutic activities.

The methodology and technology that allow the structural changes in the brains of alcoholics to be documented have only recently been turned to questions related to reversibility. With abstinence, does the brain recover? Will recovery occur if drinking continues at a reduced level? Do cognitive abilities recover? Will abstinent alcoholics eventually recover to the level of performance of nonalcoholics?

### ***Reversibility of Structural Changes***

Clinicians and scientists have generally believed that chronic alcohol abuse leads to irreversible brain damage, most often in the form of cortical atrophy. Improvements in the behavior of abstinent alcoholics were generally thought to be due to the ability of the brain to reorganize so that undamaged structures take on the functions of damaged structures. A certain amount of improvement immediately after stopping drinking was thought to be due to clearance of the toxic substance from

the brain tissue. Recent evidence has caused these beliefs to be reexamined.

The evidence comes from CT scanning of the brains of chronic alcoholics. Although the development of this technique offers exciting possibilities for research, the state of the art in its application to research with alcoholics has several major deficiencies. In addition to subject sampling and reliability problems, there are problems that result specifically from comparing two temporally separated scans on the same individual. One problem is that the expense of multiple CT scans has limited current studies to very small samples. When these samples are later divided into patients who did and did not drink between scans, the samples are so small that generalization is difficult, especially since other variables, especially age, must be controlled in such comparisons. Also, expense frequently precludes scanning the brains of normal subjects even once.

The other problem has to do with the actual measures taken from the CT scans. The procedure of hand-measuring distances that have been reduced by photography creates opportunities for error. Frequently the differences obtained by measurement are transposed into life-size so that small errors of measurement may become large enough to be mistaken for "reversibility" (Hill et al. 1979). Again, in the absence of repeat scans on normal controls, it is hard to evaluate such possibilities. A related problem is caused by the difficulty in placing the head in the scanner in exactly the same position on two occasions. A change of even a few millimeters in head position might cause either the appearance of neuroradiologic changes where none had occurred or the obscuring of changes that had occurred. Despite these methodological difficulties, the results of CT studies of reversibility suggest exciting possibilities. Reports on the three samples of alcoholics have appeared in the literature.

The first report came from researchers at the Addiction Research Foundation in Toronto, who reported a decrease in cerebral atrophy in 4 of 8 alcoholics examined with the CT scan after 2 weeks of abstinence and again 1 year later (Carlen et al. 1978). Scans were subsequently done on 15 additional patients and the data on the total sample reported (Carlen and Wilkinson 1980). The average ventricular and sulcal width was decreased in a sample of 18 patients who had been abstinent or had reduced their drinking, but the decrease was not statistically significant. Older patients tended to show less improvement on the second scan.

Ron et al. (1979) reported on 22 alcoholic patients given two CT scans approximately 1 year apart. Of these, 9 were abstinent or had reduced their drinking. The ventricle/brain ratios and ratings of sulcal widening indicated less "atrophy" at the second scan. As in the Carlen and Wilkinson study, the change was not statistically significant. Even at the second scan, the alcoholics had larger ventricles and sulci than a control group, suggesting incomplete recovery at best.



In all the papers cited above, improvement on psychological tests by at least some patients was reported. It is not clear whether these were the same patients whose CT scans showed improvement. Only Carlen et al. (1978) reported the number of patients (4 of 8) who showed improvement on both measures. Since our understanding of recovery in alcoholics will be affected by the relationship between CT measures and psychometric tests, this relationship should be examined in future research.

In light of these provocative but inconclusive reports, it is obvious that further research is required. More consistent results should appear as the CT methodology is improved and its use is standardized. Indeed, reversible structural changes in the brain as measured by CT scans are not unprecedented. Heinz et al. (1977) reported two cases of reversible cerebral atrophy in children, one with malnutrition due to anorexia and another with a pituitary tumor leading to nutritional irregularities. In both cases CT measures of atrophy were much reduced over a 7-month period. The mechanism suggested was a change in the fluid balance between brain tissue and intravascular space.

Another indication of brain plasticity is found in the report of Hill et al. (1979). The CT scans of heroin abusers revealed smaller sulci than were observed in the controls, and there was a tendency for the ventricles to be somewhat smaller. Brain plasticity is further indicated by the report by Buell and Coleman (1979). They found evidence for the growth of dendritic spines in nondemented aged subjects and lack of growth in aged subjects with senile dementia. Thus, there are precedents in the literature to suggest plasticity in the mature human brain. If reports of reversible atrophy are substantiated by future research, perhaps the term "shrinkage" (Ron et al. 1979) should be adopted to describe the phenomenon observed in alcoholics.

If reversibility does occur, what mechanisms might account for it? Carlen et al. (1978) suggested a regrowth of the brain's supportive tissues and the myelin sheaths that surround the axons of the brain, and also suggested axonal sprouting as a mechanism. Other possibilities might be reversal of ethanol-induced electrolyte shifts or dehydration in brain tissue. Carlen et al. (1979) reported unpublished data by Penn and Yasnoff indicating actual changes in brain density, which suggests an increase in tissue. If this is the case, perhaps increased protein synthesis accounts for the CT scan changes (Carlen et al. 1979). More research is necessary to substantiate and to explain the phenomenon of reversibility of structural changes in the brains of chronic alcoholics.

### *Reversibility of Cognitive Dysfunction*

Until recently, there were very few studies specifically designed to examine recoverability in alcoholics. The results of those studies indicate that different abilities recover after different lengths of time and that some deficits exist even after periods as long as a year. The appropriate methodology for studying behavioral reversibility is not

simple. Testing and retesting the same group of alcoholics may be satisfactory for the CT but not for neuropsychological tests. On the latter we must separate actual recovery from improvement resulting from practice with the testing instruments. An alternative approach is to use separate groups of alcoholics with different lengths of abstinence. This method avoids problems with practice effects, but requires extremely close matching procedures to obtain equivalent groups. Certainly sex, age, education, years of heavy drinking, and lifetime alcohol consumption are important variables to be controlled, but one can never be sure that groups have been matched on all relevant factors. Another important point has to do with evaluating the extent of recovery in alcoholics. Even if there is an increment in the performance of abstinent alcoholics, it may not be equivalent to that of nonalcoholics. Thus, a control group is a necessary part of the experimental design. Ideally, the control group should be retested so that practice effects in nonalcoholics may be evaluated. Finally, it is important to consider the time frame of reversibility. If a group of alcoholics is tested soon after detoxification and found to be improved a year later, recovery could have occurred within 1 month, 6 months, or over the entire year. Thus, multiple testing points are desirable in studies of reversibility.

Even when these factors are controlled, other problems may be encountered. Particularly in long-term studies of reversibility, one is usually forced to rely on self-reports from alcoholics on their sobriety, and such reports are likely to be unreliable. Additionally, since the rate of resuming drinking in alcoholics is extremely high, it is very difficult to find subjects with extremely long (greater than 1 year) periods of abstinence. Thus, many investigators are forced to study small samples or patients with reduced drinking rather than sobriety.

The choice of the initial testing point is another important consideration. In order to study the long-term effects of alcoholism, the patients should be studied after the withdrawal syndrome has subsided. The clinical manifestations of withdrawal typically subsided within 7 days. However, a subclinical withdrawal syndrome may persist and its effects may become entangled with the chronic effects. With our present methodology it is difficult to separate the two influences, but the question of improvement in functioning over time may still be addressed.

Few reports have dealt adequately with all of these difficulties. The limitations imposed by these problems will be noted in the conclusions we draw from the studies reviewed. Table 3 outlines the findings of nine reports that have appeared since 1976 dealing with cognitive reversibility during the first month of abstinence. Eight of the nine reports (89 percent) reported significant improvement of at least some abilities. The exception is Page and Schaub (1977) where improvement was found on only one derived measure of tactual-motor performance.

Table 3. Cognitive Recovery Within 1 Month of Abstinence

Authors (year)	Time Period Studied	Number of Alcoholic Subjects (Controls)	Age	Areas of Functioning Showing Improvement	Areas of Functioning Showing No Improvement
Goldman and Rosenbaum (1976)	5, 15, 25 days abstinence	33 (11)	43.7 (39.8)	Day 15: new vocabulary learning, verbal paired associate learning	Visual-spatial paired associated learning, learning from lecture
Sharp, Rosenbaum, Goldman, and Whitman (1977)	5, 15, 25 days abstinence	33 (11)	43.5 (37.6)	Day 15: new vocabulary <sup>1</sup> learning	
Goldman, Whitman, Rosenbaum, and Vandevusse (1978)	5, 15, 25 days abstinence	48 (16)		Day 15: cutaneous form discrimination	Cutaneous sensitivity
Page and Schaub (1977)	1 week 3 week abstinence 6 months	51	less than 60	Fine motor coordination, motor strength, bilateral transfer of training Learning aspect of tactical performance	Vocabulary, abstracting ability, perceptual motor functioning
Avers, Templar, Ruff, and Barthlow (1978)	7 days, 29 days abstinence	31	40.8	Perceptual motor speed	
Cermak and Ryback (1976)	Day of admission 1 week, 1 month	20 alcoholics 8 Korsakoff	Younger 28 (n = 10) Older 56 (n = 10) 56	Short-term memory improved only in older subjects (younger showed no deficit)	
McLaughlin, Faillice, and Overall (1979)	3-5 days abstinence 25-28 days abstinence	19	45.3	Ten subjects improved performance on visual perceptual motor abilities (young, shorter term drinkers)	Nine subjects remained impaired on visual perceptual motor abilities (older, longer term drinkers)



Table 3. Cognitive Recovery Within 1 Month of Abstinence

Authors (year)	Time Period Studied	Number of Alcoholic Subjects (Controls)	Age	Areas of Functioning Showing Improvement	Areas of Functioning Showing Improvement
Eckardt, Parker, Noble, Pautler, and Gottschalk (1979)	7, 17, 21 days	123 (20)	41.4 (45.6)	Tactual-motor and visual-perceptual-motor abilities	Nonverbal abstraction, perceptual-motor speed visual-spatial memory
Kish, Hagen, Woody, and Harvey (1980)	6, 15, 21, 110 days abstinence	107	45.4	Day 15: perceptual motor abilities, short-term memory, abstracting ability	

1. Performance equaled that of control group.

The table indicates that there are different recovery rates for different abilities. Verbal abilities appear to recover at a faster rate than nonverbal abilities. As indicated in the studies by Goldman (in press) and his associates, verbal deficits are limited primarily to new vocabulary learning and seem to disappear after approximately 2 to 3 weeks of abstinence. Similar improvement is seen in pure sensory and motor capacities.

More complex abilities such as short-term memory and visual-spatial learning show somewhat less improvement within a month's time. Even more complex nonverbal abstracting ability and perceptual-motor abilities remain impaired, particularly in some patients. Older patients with a longer period of alcohol abuse show the least improvement. Our enthusiasm over the high percentage of studies reporting some level of recovery must be tempered by another consideration. What level of reversibility can be expected after 1 month of abstinence? Only four of the reports outlined in table 3 included data from control subjects. In two of these (67 percent), the alcoholics attained a level of performance equal to that of the controls in one area, new vocabulary learning. Since most of the studies did not include a control group it is difficult to properly evaluate this issue, but the evidence suggests that significant impairment remains after 1 month of abstinence.

Table 4 contains a description of six studies that examined various aspects of cognitive reversibility over periods of 1 month to 6 months. In four of these studies the initial tests took place after 2 to 3 weeks of abstinence, so that much of the recovery of verbal abilities observed over this time period had already occurred. Two of the studies were considered in the previous section. Of the six studies there is evidence for significant improvement in four (67 percent). The data suggest that the abilities most impaired at the end of 1 month, i.e., nonverbal abstracting ability and perceptual-motor abilities, recover to limited extent between 3 and 6 months. In the two studies that included a control group, the data suggest that the alcoholics examined remained impaired relative to controls in some areas.

Remarkably similar results have been reported in studies that examined reversibility over periods of 1 year or longer. The six studies that have appeared in the literature are described in table 5.

Table 4. Cognitive Recovery Between 1 and 6 Months of Abstinence

Authors (year)	Time Period Studied	Number of Alcoholic Subjects (Controls)	Age	Abilities Recovered	Abilities Showing No Recovery
Carlen and Wilkinson (1980)	3 weeks 15 weeks	53	45	WAIS verbal, performance and full scale IQ; Wechsler, Memory Scale Score	
Jenkins and Parsons (1980)	3 weeks 12 weeks	48 (24)	46.5 (45.9)	Abstracting ability	Response perseveration
Leber, Jenkins, and Parsons (in press)	3 weeks	32 (16)	49.7 (49.2)	Visuospatial paired associate learning; visuospatial memory	Response perseveration
Kish, Hagen, Woody, and Harvey (1980)	6,15,21, 110 days	107	45.4	Day 15: perceptual motor abilities, short-term memory, abstracting ability	No significant improvement in 21- and 110-day groups
Page and Schaub (1977)	1 week 3 weeks 6 months	51	Less than 60		Vocabulary, abstracting ability, perceptual motor motor functioning
Guthrie and Elliott (1980)	2 weeks 6 months	35	Age of retested Sample not reported	Specific test scores not reported; authors report improvement	



Table 5. Cognitive Recovery Following Extended Periods of Abstinence

Authors (year)	Time Period Studied	Number of Alcoholic Subjects (Controls)	Age	Abilities Showing At Least Partial Recovery	Abilities Showing No Recovery
Long and McLachlan (1974)	1 year abstinence	17 (22)	44.5 (44.6)	Visual-perceptual motor skills, abstracting ability, tactual performance	Perceptual motor speed
O'Leary, Radford, Chancy, and Schau	2 weeks abstinence	24 (20)	51.0 (49.9)	Perceptual motor speed	
Schau, O'Leary, and Chancy (in press)	2 weeks 14 months	27 (27)	50.4 (49.4)	Visual perceptual-motor and perceptual motor speed	Abstracting ability, tactual-motor ability
Hill, Reyes, Mikhael, and Ayre (1979)	less than 2 months 12.5 months	23 (14)	34.7 (28.8)		Abstracting ability, tactual-motor ability
Grant, Adams, and Reed (1979)	3 weeks abstinence 18 months abstinence	82 (40)	37.1 (37.0)	No impairment demonstrated on initial testing	
Berglund, Leijonquist, and Horlen (1977)	3.7 years	53 (32)	46.0 (40)	Visual-perceptual motor ability and verbal paired associate learning—visual retention	Adaptive ability
Fabian, Parsons, and Silberstein (1980)	4 years	40 (female) (70)	42.3 (42.5)	Nonverbal abstracting, perceptual-spatial, motor, problem-solving	Perceptual motor speed

Again, 67 percent of the studies indicate improvement, especially in abstracting and visual-perceptual motor abilities. The two studies that found no evidence of improvement differed from the other studies in several methodologically important ways. In both studies, the age of the alcoholics was considerably lower than in the majority of reports in the alcoholism literature. Grant et al. (1979) found no evidence of impairment in their alcoholics and, thus, would be hard put to demonstrate recovery. The subjects of the study by Hill et al. (1979) were highly variable in their lengths of abstinence so that the average length of abstinence of 12.5 months for one group is not representative of the entire group. Thus the negative results of these studies are questionable. Regardless of the difficulties with two of the studies, there is striking consistency among the reports listed in table 5 in that none of the alcoholic samples tested attained a level of performance equal to that of the control subjects.

In view of these findings, the answer to the question posed at the beginning of this section—Do the cognitive abilities of alcoholics recover?—is a qualified “yes.” At least partial recovery occurs in a wide range of abilities, but it is possible that the deficits that remain after a year or longer are permanent.

One puzzling aspect of the research reviewed above is that in three studies improvement in test performance was often noted even when alcoholic patients begin drinking again. The designs of the experiments involved were such that practice effects might be part of the explanation; however, with retest intervals as long as a year the influence of practice should be minimal. Several other explanations should be considered. It is possible that a prolonged period of abstinence, such as occurs when a patient enters a treatment program, allows a certain amount of recovery that has not completely dissipated by the time of the followup test. It is also possible that an extended period is required for an alcoholic who resumes drinking to regain the previously high level of consumption. Cognitive gains that resulted from treatment might last a considerable period of time in alcoholics who are drinking at a reduced level. These and other possibilities will have to be evaluated in future research.

In summary, the questions surrounding reversibility of brain and cognitive dysfunction in alcoholics are critically important for understanding the effects, treatment, and outcome of the disorder. The present evidence for reversibility is encouraging but not clearly established. Methodologically sophisticated studies with long-term followup are urgently needed.

## ***Current Status and Future Research Directions***

### *Current Status*

We are now in a position to present the current answers to the questions posed earlier concerning the effects of alcohol on the brain.

Which brain structures are affected?

Pneumoencephalographic and CT scan data indicate a significant degree of atrophy (loss of brain cells) in the brains of alcoholics. Evidence for both cortical (sulcal widening) and subcortical (ventricular enlargement) atrophy is present. It is likely that the atrophy is diffuse, so that many brain structures are involved. In Intermediate Stage alcoholics, approximately 50 to 70 percent have such abnormalities and older alcoholics show more brain abnormality than younger alcoholics.

Which cognitive abilities are affected?

Our review indicates that alcoholics are mildly but significantly impaired in problem-solving, nonverbal abstracting, and perceptual-motor-spatial abilities. These deficits are limited; general verbal and performance intelligence levels are in the average to above average range.

Are cognitive deficits different in men and women?

Although little data have been reported on the neuropsychological performance of female alcoholics, it appears that their pattern of impairment is the same as in males.

Does alcohol prematurely age the brain?

The structural abnormalities in alcoholics resemble those in elderly patients, and many of the behavioral deficits are similar in the two groups. However, the structural similarities do not necessarily imply similar underlying processes. Much more research will be necessary to determine the degree of identity between aging and the effects of alcohol abuse.

Are heavy social drinkers likely to have deficits similar to those in alcoholics?

This is another topic that has received little attention in the scientific literature. The reports that have appeared indicate that moderate to heavy social drinking may be related to deficits similar to those in alcoholics, although the level of deficit is less. The available evidence is far from conclusive.



With abstinence, does the brain recover?

Data from several small samples of alcoholics suggest that positive changes (decrease in atrophy?) occur in the brains of alcoholics after a year of abstinence. The changes observed are small and there are methodological problems with the research. If such changes do occur, the mechanism that would account for them is unknown.

Do cognitive abilities recover?

The majority of research indicates that improvement in cognitive functioning may be observed over periods ranging from 3 weeks to 1 year. There is no evidence to suggest that alcoholics reach a level of functioning equal to nonalcoholics across all abilities, regardless of length of abstinence. Age may be an important factor; older alcoholics may not recover to the same extent as younger alcoholics.

Are there different recovery rates for different mental processes?

Certain abilities seem to recover sooner than others. The earliest improvement is in tasks with a verbal component, e.g., new verbal learning. Other more complex and less practiced abilities, e.g., nonverbal abstracting and adaptive abilities, may be impaired even after a year or more of abstinence.

### *Future Research Directions*

Given our current knowledge of alcohol's effects on the brain, it is clear that further research is necessary. In the biomedical area, the greatest strides will come from technological and methodological improvements in the use of the CT scans to study alcoholics. Larger samples of alcoholics and standardized measurement techniques will be necessary to answer many of the questions posed by current research. Two other biomedical techniques, the recording of event-related potentials and the measurement of cerebral blood flow, offer exciting possibilities for future research because they allow one to study the brain in action. As these techniques become more generally applied, it should be possible to examine relationships between behavioral measures and direct biological measures of the brain's functioning.

Improved measurement techniques and new areas of exploration should also be the future directions in the behavioral sphere. It is desirable to develop tasks and techniques to distinguish the effects of alcohol abuse from other influences that compromise brain function, particularly the aging process. Further behavioral research is also required to discover alcohol's effects on cognitive abilities in women. The effects of social drinking should be more fully explored to define the more harmful drinking practices.

Large-scale in-depth investigation of reversibility of the brain's altered structure and function and behavioral changes should have high priority in future research on alcoholism. Many methodological problems associated with the research on brain reversibility need to be resolved. More long-term followup studies on alcoholics are needed to plot the course of recovery and to discover what variables might determine how much reversibility is possible. Especially important is the identification of neuropsychological variables related to therapeutic progress and prediction of recovery. Relationships between perceptual motor functioning and ratings of predicted prognosis have recently been reported (Leber and Parsons 1980). If relationships are found between these variables and actual outcome measures, perhaps some predictive principles may be developed.

The resumption of drinking by alcoholics is a persistent and nagging problem in alcohol treatment programs. In the Intermediate Stage alcoholics who constitute the bulk of patients in treatment programs, what causes patients to resume this potentially crippling and even lethal drinking behavior? Research has revealed that personality variables, social functioning at intake, and posttreatment environment explain only a small part of treatment outcome (Finney et al. 1980). It may be that neuropsychological functioning (i.e., poor abstracting and problem-solving abilities) would account for an additional portion of this variability. To our knowledge this problem has not been investigated systematically.

Finally, future research also must address the question of what approaches might be used to ameliorate permanent neuropsychological deficits. Are there cognitive retraining techniques that would be successful with alcoholics? There is currently very little evidence bearing on the issue. Cermak (1980) has reported limited success in improving the memory capabilities of alcoholic Korsakoff patients by training them in the use of visual images and verbal cues. A more clinically oriented training program has been developed in Denmark by Hansen (1980). She describes a series of training sessions with alcoholics aimed at improving their motor coordination, attention, abstract thinking, spatial functions, and memory. No formal assessment of these abilities at the end of the program has been undertaken, but the patients report improved memory and self-esteem as a result of participating in the program. It would appear that this is a promising and important area for future research.

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## **Chapter 8**





# The Wernicke-Korsakoff Syndrome

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## Abstract

The Wernicke-Korsakoff syndrome is a neurological syndrome that can occur in chronic alcoholics. During the acute Wernicke stage the symptoms include a global confusional state, optic abnormalities, ataxia, and polyneuropathy. In the chronic Korsakoff stage of the disorder a severe amnesic condition, consisting of both anterograde and retrograde memory loss, is the disease's most significant feature.

During the past 10 years numerous investigations concerned with the neuropsychological, neuropathological, and etiological factors involved in alcoholic Korsakoff's syndrome have been published. The neuropsychological research has focused upon the patient's severe memory deficits, and several theories based on current models of human information processing have been advanced. One theory has stressed the Korsakoff patient's increased sensitivity to proactive interference, while others have emphasized the patient's deficits in stimulus and contextual encoding. Neuropathological investigations have continued to implicate midline diencephalic structures in the chronic symptoms of this disorder, and some very recent studies have begun to assess the role of various neurotransmitters in the patient's memory impairments. These latter studies offer some hope for ameliorating some of the patient's cognitive deficits.

The etiology of the syndrome also appears to be more complex than one believed. The neural damage associated with the Wernicke-Korsakoff syndrome has traditionally been attributed to a deficiency in thiamine, but recent animal studies demonstrating the neurotoxicity of alcohol have suggested that the amnesic symptoms may be due to an interaction of malnutrition and the toxic effects of alcohol. Behavioral studies reporting that non-Korsakoff alcoholics have memory deficits qualitatively similar to those of Korsakoff patients support the idea that Korsakoff's syndrome is not acute, but may develop slowly during decades of alcohol abuse.

## Introduction

In 1881, Carl Wernicke described in three patients (two men with alcoholism and one woman with sulfuric acid poisoning) a neurological syndrome that included ataxia, optic abnormalities, and a confusional state. Postmortem examination of these three patients showed small

punctate hemorrhages symmetrically located in the gray matter around the third and fourth ventricles of the brain. Wernicke characterized this disorder, which now bears his name, as an acute inflammatory disease of the ocular-motor nuclei and noted that the symptoms were progressive and led to death in approximately 2 weeks. Six years after the publication of Wernicke's paper, S. S. Korsakoff published the first of a series of reports in which he detailed the amnesic and confabulatory symptoms that often accompanied disorders involving polyneuropathy. While long-term alcoholism often preceded these mental changes, Korsakoff noted that the symptoms also followed a number of other conditions such as persistent vomiting, typhoid fever, and intestinal obstruction. On the basis of his observations, he concluded that the presence of a substance toxic to the peripheral and central nervous systems must have been the common denominator in these cases. Although neither Wernicke nor Korsakoff could be specific about etiology, and both seemed unaware that their two syndromes often occurred sequentially in the same patients, their clinical descriptions of their patients' symptomatology were accurate and represented important initial steps in the identification and understanding of the Wernicke-Korsakoff syndrome.

The major symptoms of the Wernicke stage include a global confusional state, ophthalmoplegia, nystagmus, ataxia, and a polyneuropathy (e.g., pain, loss of sensation, weakness) of the legs and arms (Victor et al. 1971). Of these neurological symptoms, the global confusional state is perhaps most germane to our interests. The patient is disoriented as to time and place, unable to recognize familiar people, apathetic, inattentive, and, most significantly, unable to maintain a coherent conversation.

The patient with a Wernicke encephalopathy, if not treated with large doses of thiamine, is in danger of having fatal midbrain hemorrhages. If the patient does receive proper vitamin therapy, however, the neurological symptoms will improve markedly. In most cases, the ocular problems will almost disappear, the ataxia and peripheral neuropathies will improve, and the confusional state will clear. After 2 or 3 weeks of thiamine treatment, the patient will realize that he is in a hospital, recognize family members, and be able to converse intelligibly with the physician. At this point, the patient has passed the acute Wernicke phase and has entered the chronic Korsakoff stage. Very few Wernicke patients show a complete recovery to their premorbid intellectual state (Victor et al. 1971).

### ***Anterograde Amnesia of Alcoholic Patients With Korsakoff's Syndrome***

The most striking feature of alcoholic Korsakoff patients is *anterograde amnesia*—the inability to learn new verbal and nonverbal



information from the time of onset of illness. For the Korsakoff patient, learning the name of the physician, the nurse, or the hospital, and even the location of his bed, may require weeks or months of constant repetition and rehearsal. Events that occurred hours or even minutes before will be lost. Not only does this patient fail to learn the names of important people and places, but often he will not remember previous encounters with these individuals. If the patient spends 3 hours completing a number of psychometric tasks, he will fail to recall the entire test session 2 hours after it has ended. Three common words read to the patient cannot be recalled 10 seconds later (Butters and Cermak 1976; Cermak and Butters 1973). As one patient described his existence, "I always feel as though I am just waking up. I don't remember what happened a minute ago. I don't know the meaning of what's going on."

Experimentally, this severe anterograde problem is exemplified by the severe difficulty Korsakoff patients have in learning even short lists of five or six paired-associates (Ryan and Butters 1980a; Winokur and Weiskrantz 1976). When an alcoholic Korsakoff patient is shown a list of word pairs (e.g., man-hammer) in which he must learn to associate the second word with the first, the acquisition of these associations may require 30 or 40 trials instead of the 3 or 4 presentations needed by intact subjects.

Since the publication of Talland's (1965) monograph, the vast majority of neuropsychological studies concerned with alcoholic Korsakoff's syndrome have centered on the processes underlying this profound inability to learn new information (Butters and Cermak 1975, 1976, 1980; Cermak and Butters 1973). Most investigators have consistently found that alcoholic Korsakoff patients are impaired in short-term memory or in the transfer of information from short- to long-term storage (Butters and Cermak 1976; Kinsbourne and Wood 1975; Piercy 1977). If alcoholic Korsakoff patients are presented (visually or orally) with three words (e.g., apple, pen, roof) and then required to count backwards from 100 by 3s to prevent rehearsal (i.e., a distractor task), they will be impaired in the recall of the three words after only 9 or 18 seconds of such counting activity. While there is some evidence that the Korsakoff patients' nonverbal short-term memory is superior to their verbal retentive capacities (Butters et al. 1973), it now appears that this superiority is related to the verbal nature of the distractor activity. Counting backwards is a verbal task, and it interferes more with verbal than with nonverbal materials. The introduction of a nonverbal distractor activity can lead to better performance with verbal than nonverbal materials (DeLuca et al. 1976).

### *The Proactive Interference Hypothesis*

The importance of the distractor task for the Korsakoff patients' performance exemplifies one of the most prominent features of their anterograde amnesia: increased sensitivity to proactive interference, in

which patients are unable to acquire new information because of interference from previously learned materials. The evidence for this interference stems from three sources: (1) the nature of the Korsakoff patient's errors on learning tasks (Meudell et al. 1978); (2) demonstrations of normal performance when partial information is provided at the time of retrieval (Warrington and Weiskrantz 1970, 1973); and (3) demonstrations of improved retention when the learning conditions are structured to reduce proactive interference (Butters and Cermak 1975).

Although Korsakoff patients are severely impaired on short-term memory (distractor) tasks, this impairment is not manifested in an equivalent manner throughout the test session. On early trials in a session the patients will often perform normally, but their recall will deteriorate very rapidly on subsequent trials. It has been shown that Korsakoff patients may recall as much as 90 percent of the presented materials on trials 1 and 2 but may recall less than 50 percent of the information shown on trial 5 of the session (Cermak et al. 1974). This rapid drop in performance seems related to a rapid increment in proactive interference. On trial 5 the patient is still recalling the material presented on trials 1 and 2. These intra-list intrusions suggest that the learning of material on trials 1 and 2 is hindering the patient's attempts to recall the stimuli from trial 5.

Meudell et al. (1978) compared the types of errors made by Korsakoff patients, demented patients with Huntington's Disease, and normal control subjects on a short-term memory distractor task. They found that the Korsakoff and the demented patients made numerous errors on the tests but that the types of errors they produced differed significantly. The Korsakoff patients' errors were primarily intrusions from prior list items while the patients with Huntington's Disease made many omission errors (i.e., a failure to make any response). Interference then does not appear to be a crucial factor in the memory disorders of all brain-damaged patients.

With methods of retrieval that reduce interference, the performance of alcoholic Korsakoff patients may not differ from that of normal controls. Warrington and Weiskrantz (1970) have shown that while amnesics are severely impaired when unaided recall or recognition tests are employed, they do retrieve normally when partial information, such as the first two letters of the to-be-remembered words, is provided. Warrington and Weiskrantz (1973) believe that the superiority of the partial information method stems from the limitations it places on interference from previously learned information. If the first two letters of the to-be-recalled word are "ST," the number of words that can possibly interfere with the recall of the target word "STAMP" is greatly limited. Apparently, free recall and recognition procedures do not limit proactive interference to the same degree.

It is well known from the literature on normal human memory that proactive interference may be reduced by specific manipulations of the conditions under which learning is attempted. For example, distributed practice results in less interference than does massed practice. Also, a



consonant trigram (e.g., J R N) will interfere less with the retention of a word triad (e.g., rose, ship, camel) than will another word triad (e.g., tulip, car, horse). When the distractor task was administered with distributed presentation (1 minute rest between successive trials) rather than massed presentation (6 seconds between trials) to alcoholic Korsakoff patients, patients with Huntington's Disease, and alcoholic controls, the Korsakoff patients and the controls showed significant improvements in their performance (Butters et al. 1976). In fact, the Korsakoff patients recalled as many items with distributed practice as the controls did with massed practice. However, this reduction in interference by means of distributed trials had no effect on the memory deficits of the demented Huntington's patients; they performed as poorly with distributed as with massed practice. Almost identical results have been found when a word triad was preceded by a consonant trigram rather than another word triad (Butters et al. 1976). Again, low interference conditions led to improvement in the short-term memory of alcoholic Korsakoff patients and normal controls but to no changes in the poor performances of patients with Huntington's Disease.

### *The Limited Encoding Hypothesis*

While Warrington and Weiskrantz (1973) have been content to accept interference as an explanation of amnesia, other investigators have viewed the "interference theory" as primarily descriptive rather than explanatory (Piercy 1977) and have offered hypotheses to account for both the patients' retention and interference problems. Butters and Cermak (1974, 1975, 1976, 1980) have suggested that Korsakoff patients' verbal memory impairment is related to a failure to encode, at the time of storage, all of the attributes of the stimulus. Korsakoff patients may fully categorize verbal information according to its phonemic and associative attributes, but they seem inadequate in their analysis of the semantic features of the materials. Information that is not fully analyzed (encoded) may be stored in a degraded fashion and thus be more sensitive to interference. The evidence supporting this conclusion stems from cueing studies in which phonemic (e.g., rhymes) and semantic (e.g., superordinate) cues were compared in terms of their ability to facilitate recall. In general, phonemic cues worked as well for alcoholic Korsakoff patients as for controls, but semantic cues aided the recall only of the control subjects. While the results of some studies have been consistent with the semantic encoding hypothesis (Cermak and Moreines 1976; Cermak and Reale 1978; Cermak et al. 1974), the findings of other investigations have not confirmed this theory (Winokur and Weiskrantz 1976).

To determine whether alcoholic Korsakoff patients' deficits in semantic encoding might represent a specific example of a more general limitation in the ability to extract the features of complex stimuli, Glosser et al. (1976) employed a modified version of the dichotic listening technique with alcoholic Korsakoff patients, chronic alcoholics,



and normal controls. Their dichotic techniques involved a simultaneous presentation of two single digits to the patient, one to the right ear and one to the left. The patient was instructed to press a response key whenever the digit pairs had certain preselected spatial and/or identity features.

Under Condition 1, patients were instructed to press the response key if the number "10" was presented to their right (or left) ear. Under Condition 2, the patients were to respond if the critical number "10" appeared in either ear. Condition 3 required the patient to respond only when the digit pair "9-10" appeared simultaneously in both ears. If one of the two critical digits was paired with a noncritical digit (e.g., "7"), the patients were instructed not to respond. Condition 4 required the patients to respond only when the digit "9" occurred in the right (left) ear and "10" in the left (right) ear. For all these conditions the interval between successive pairs of digits was 1.2 seconds. For Conditions 5 and 6 (virtually repeats of the third and fourth conditions), the interpair interval was increased from 1.2 seconds to 2.0 seconds.

The results of Glosser et al.'s (1976) study show that the alcoholic Korsakoff patients did not differ significantly from the normal controls on Conditions 1 and 2, but on Conditions 3 and 4 the differences between these two groups were significant. It might also be noted that except for their unexplainable difficulty with Condition 1, the alcoholics showed the same pattern of deficits as the alcoholic Korsakoff patients. As more and more features of the dichotic stimuli had to be processed, the Korsakoff patients and the chronic alcoholics became increasingly impaired. On Conditions 5 and 6, both alcoholics and Korsakoff patients improved their performance but continued to make more errors than the normal controls.

The pattern of commission errors made by the alcoholic Korsakoff patients in Condition 4 suggests the nature of their difficulty on these dichotic tasks. They made no more errors than the normal controls when both dichotically presented digits were noncritical (e.g., "3" in the right ear, "8" in the left ear). However, when only one of the critical digits was present, or when the ear placement of the two critical digits was inverted, the Korsakoff patients made many more errors than did the normal controls. It appeared that when the decision processes became complicated, the Korsakoff patients did not fully analyze all the incoming information. They failed to process both channels of inputs and/or failed to process both stimulus dimensions (phonemic, spatial).

The alcoholic Korsakoff patients' impairments on Conditions 3 and 4 of this experiment further confirm the hypothesis that they have a general deficit in analyzing or processing all the dimensions of new information. Whether the stimuli be visual patterns (Oscar-Berman and Samuels 1977), names of common items (Cermak, Butters, and Gerrein 1973), or digits presented dichotically (Glosser et al. 1976), alcoholic Korsakoff patients have difficulty processing all of the features of the stimuli. Glosser et al.'s experiment also suggests that what processing Korsakoff patients can perform takes longer than normal. Given

additional time to process information (Conditions 5 and 6), the performance of alcoholic Korsakoff patients does improve. This fact had also been observed previously (Cermak et al. 1974) on a task in which patients were required to determine whether or not an "A" and an "a" had the same name. Under these conditions Korsakoff patients took longer to respond than did controls.

Most recently, the limited encoding hypothesis has been applied to some of the alcoholic Korsakoff patients' nonverbal cognitive deficits. In addition to their problems with verbal memory, alcoholic Korsakoff patients are significantly impaired on a number of visuoperceptive tasks such as retention of random geometric forms (DeLuca et al. 1975), digit-symbol substitution tasks (Glosser et al. 1977; Kapur and Butters 1977; Talland 1965), hidden figure tests (Glosser et al. 1977; Kapur and Butters 1977; Talland 1965) and visual card sorting (Oscar-Berman 1973; Oscar-Berman and Samuels 1977). Oscar-Berman and Samuels (1977) provided some evidence that alcoholic Korsakoff patients' perceptual problems may reflect an incomplete analysis of all attributes of visual stimuli. Such patients were trained to discriminate between complex visual stimuli differing on a number of relevant dimensions (e.g., color, form, size, position) and then were administered transfer tasks to determine which of the relevant stimulus dimensions had been noted. While the intact controls showed transfer to all of the relevant stimulus dimensions, the Korsakoff patients' discriminations were based upon only one or two relevant features of the stimuli.

Dricker and her colleagues (1978) provided further evidence for this "limited analysis" hypothesis in a study of face perception. Alcoholic Korsakoff patients, detoxified alcoholics, and non-alcoholic controls were administered a facial matching task that compared the subjects' tendency to use superficial piecemeal cues (such as paraphernalia and expression) and more advanced configurational cues in their analyses of faces. Configurational cues refer to the spatial relationships among the nose, mouth, and eyes. The results showed that alcoholic Korsakoff patients often matched faces (i.e., judged them to be identical) on the basis of paraphernalia (e.g., hats) and expression while normal controls and alcoholics relied on the traditional and correct configurational cues. It appeared then that the Korsakoff patients did not analyze all of the relevant features of unfamiliar faces. While normal subjects utilize configurational features of faces, the Korsakoff patients rely upon more piecemeal or superficial features such as paraphernalia and expression and seem to ignore the configurational features of faces. If such limited perceptual analysis is characteristic of alcoholic Korsakoff patients, it may at least partially explain their difficulties in learning, remembering, and even perceiving nonverbal patterned materials. Just as Korsakoff patients may fail to retrieve verbal material because of faulty or incomplete encoding, so a similar impairment in perceptual processing may be responsible for their nonverbal visual memory and perceptual deficits.



*The Limited Contextual Encoding Hypothesis*

While some investigators (Butters and Cermak 1976; Cermak and Butters 1973) have stressed a general limitation in encoding as the source of the Korsakoff patients' amnesic problems, other investigators (Huppert and Piercy 1976; Kinsbourne and Wood 1975; Winokur and Kinsbourne 1978) have suggested that such memory deficits reflect a specific failure to encode the contextual attributes of new information. That is, alcoholic Korsakoff patients may be able to encode many of the specific physical or semantic attributes of a stimulus but fail to note the temporal and spatial contexts in which the stimulus was encountered. As a consequence of this deficit, these patients may later recognize the stimulus as familiar but be unable to "recall" when or where they experienced the stimulus. This hypothesis is consistent with the frequent clinical observation that Korsakoff patients can accurately select from a room full of people those individuals they have seen before but are unable to recall under what circumstances the interaction occurred. Huppert and Piercy (1976) have provided some experimental evidence for this hypothesis. They presented Korsakoff patients and control subjects with a series of familiar and unfamiliar pictures and later asked them to select the ones that had been exposed previously. While the Korsakoff patients were impaired for both familiar and unfamiliar pictures, their performance was much better with the unfamiliar pictures. The investigators believe that this disparity in performance was due to the fact that familiar, but not unfamiliar, pictures require the patients to make a contextual judgment. For the correct identification of an unfamiliar stimulus the Korsakoff patient only has to determine whether he has, or has not, seen the picture before. However, for correct identification of a familiar picture the patient must not only determine that he has seen the picture previously (i.e., that it is familiar) but also whether the familiar picture has been included in the series administered by the investigator. The patients' failures with the familiar pictures are supposedly due to their inability to associate the pictures with the testing context.

Winokur and Kinsbourne (1978) have supplied additional evidence for this contextual encoding hypothesis. Amnesic patients were required to learn lists of verbal paired associates under conditions that maximized the interference between successive lists (e.g., both lists contained the same stimulus but different response elements). While this proactive interference made learning almost impossible for the alcoholic Korsakoff patients, their performance could be greatly improved by increasing the saliency (e.g., use of different colored inks, background music) of the contextual cues in the learning environment.

It should be noted that the application of information processing concepts to neuropsychological studies of amnesia is relatively new and that a solid empirical base upon which to develop theories is still lacking. Few should be surprised, then, that all of the currently popular hypotheses of amnesia are deficient in their explanation of the myriad



symptoms associated with the alcoholic Korsakoff symptoms. Complete and valid theories must await a more thorough empirical knowledge of the Korsakoff patients' performance on various cognitive tasks.

## ***Retrograde Amnesia of Alcoholic Patients With Korsakoff's Syndrome***

### *Temporal Gradients in Retrograde Memory Deficits*

Retrograde amnesia is also a distinct and consistent feature of Korsakoff's syndrome. The patient has trouble retrieving from long-term memory events that occurred prior to the onset of his illness. When asked who was President of the United States before Mr. Nixon, the patient might answer "Truman" or "Eisenhower." In 1975, researchers asked a recently diagnosed Korsakoff patient if the United States was still at war. The patient replied, "I think they have that war in Korea all wrapped up." In general, this difficulty in retrieving old memories is usually more pronounced for events just prior to the onset of the illness, while remote events from the patient's childhood and early adulthood are well remembered. Most alcoholic Korsakoff patients who served in World War II can describe their tours of duty with great detail and apparent accuracy but are unable to recall any of the major public events (e.g., the assassinations of the Kennedy brothers, Vietnam War protests) of the 1960s.

This temporal "gradient" is not only evident during a mental status examination but has been demonstrated in numerous experimental studies. Seltzer and Benson (1974) used a multiple-choice questionnaire and found that their alcoholic Korsakoff patients could remember famous events from the 1930s and 1940s better than events from the 1960s and 1970s. Marslen-Wilson and Teuber (1975) presented alcoholic Korsakoff patients with photographs of famous people and found that the patients had much more difficulty identifying famous faces from the 1960s than faces from the 1930s and 1940s.

Warrington and her associates have challenged the existence of this gradient and have presented evidence that amnesic patients have as much difficulty retrieving remote (e.g., childhood) events as recent events. Sanders and Warrington (1971) administered a "famous events" questionnaire and a test of famous faces to five patients with amnesia (mixed etiology). Their patients were impaired relative to the control group on all tests and for all periods of time. Unlike the impairment observed in the studies reviewed above, the patients' impairment was equally severe at all time periods. Warrington believes that the difference between her results and those of other studies is related to the relative difficulty of the test items. That is, while Warrington attempted to ensure that items from different decades were of equal difficulty (i.e., she chose people and events whose fame did not extend beyond a single decade), such controls were not evident in other

studies of retrograde amnesia. It is, according to Warrington, entirely possible that the temporal gradients described by other investigators (Marslen-Wilson and Teuber 1975; Seltzer and Benson 1974) may be due to the fact that questions and faces from the 1930s and 1940s were easier to answer or recognize than those from the 1960s and 1970s.

Albert et al. (1979) have recently reexamined retrograde amnesia in light of Warrington's criticisms of other studies. They developed three tests—a famous faces test, a recall questionnaire, and a multiple-choice recognition questionnaire. Each test consisted of items from the 1920s to the 1970s that had been assessed on a large population of normal controls before inclusion in the final test battery. Half of the items were “easy” as judged by the performance of the standardization group; the other half were “hard” as judged by the same criterion. The “easy” items all concerned people or events whose fame spanned many decades (e.g., Charlie Chaplin, Charles Lindbergh) and the “hard” items concerned people or events whose fame was limited to 1 decade (e.g., Tiny Tim, Rosemary Clooney). In addition to the “easy-hard” dichotomy, the famous faces test included photographs of some individuals early and late in their careers. For example, photographs of Marlon Brando from the 1950s and the 1970s were both included in the test battery.

When this retrograde battery was administered to a group of 11 alcoholic Korsakoff patients and a group of 15 normal controls matched to the amnesics for age and educational background, little evidence supporting Sanders and Warrington's (1971) contentions were found. Rather, the classical gradient was evident regardless of the difficulty of the items. For both “easy” and “hard” items, the alcoholic Korsakoffs identified more photographs from the 1930s and 1940s than from the 1960s. On the recall questionnaire the same gradients emerged.

When Albert et al. assessed the patients' ability to identify photographs of famous people early and late in their careers, further evidence for the sparing of remote memories was found. While the normal controls were more accurate at identifying famous people later than earlier in their careers, the alcoholic Korsakoff patients performed in the opposite manner. The Korsakoffs were more likely to identify Marlon Brando as he appeared in the 1950s than as he looked in the late 1960s or early 1970s.

Meudell et al. (1980) developed a retrograde amnesia test consisting of voices of famous people recorded in the last 50 years. When this task was administered to patients with alcoholic Korsakoff's syndrome and control subjects, the results were similar to those reported with questionnaires and photographs of famous faces. The Korsakoff patients showed a retrograde amnesia for voices extending over several decades and a relative preservation of memories for the more remote past. When subjects were asked to assign identified voices to their correct recorded decade, the alcoholic Korsakoff patients were significantly impaired in comparison to the normal control subjects.

On the basis of the Albert et al. study and the other investigations reviewed, it seems fair to conclude that temporal gradients do

characterize the retrograde memory deficits of alcoholic Korsakoff patients. Whether the gradients reported for alcoholic Korsakoff patients (Albert et al. 1979; Marslen-Wilson and Teuber 1975; Seltzer and Benson 1974) are also characteristic of other groups of amnesic patients (e.g., postencephalitics) is highly questionable. Some preliminary studies (Butters 1979; Butters et al. 1979) have suggested that retrograde amnesia is not a unitary disorder and may be manifested in different forms depending on the etiology of the neurological illness. For example, both patients with Huntington's Disease and patients whose amnesia is related to herpes encephalitis have retrograde amnesias that are more severe and "flatter" (i.e., no temporal gradient) than those of alcoholic Korsakoff patients.

### ***Confabulation of Alcoholic Patients With Korsakoff's Syndrome***

The alcoholic Korsakoff patients' tendency to *confabulate* when faced with questions they cannot answer is often cited as a characteristic of their disorder. When asked to recall his activities of the previous day, a Korsakoff patient may "fill in" this gap in his memory with a story concerning a trip to his home or to a sporting event that may actually have occurred many years ago. This confabulatory tendency is not a constant or necessarily permanent feature of amnesic patients, and there are marked individual differences among amnesic populations. In general, confabulation is most marked during the acute stages of the illness and becomes progressively less noticeable as the patient adjusts to his disorder. It is relatively easy to elicit confabulation from a patient in a Wernicke-Korsakoff confusional state, but such responses are rare in chronic Korsakoff patients who have had this disease 5 or more years. Certainly the notion that confabulation is a cardinal symptom of Korsakoff's disorder is not consistent with most experiences with such patients.

### ***Psychometric Features of Alcoholic Patients With Korsakoff's Syndrome***

#### ***Intelligence***

Despite the severity of the Korsakoffs' memory impairments, their intellectual functions as measured by standardized IQ tests often remain relatively intact (Butters and Cermak 1976, 1980). Thus it is important to distinguish at this point the alcoholic Korsakoff patients from patients with alcoholic dementia. The latter patients demonstrate a general and severe intellectual decline associated with decades of alcohol abuse, and their memory problems do not stand out as their



most noticeable and debilitating symptom. Table 1 shows the performances of nine alcoholic Korsakoff patients and nine intact normal controls on the Wechsler Adult Intelligence Scale (WAIS). The two groups have been matched on the basis of age (mean = 53 years), socioeconomic class (working class), and educational background (mean = 11 years of formal education). Except for the digit-symbol subtest, there are no significant differences between the Korsakoff patients and the normal control subjects. Special notice should be made of the Korsakoffs' normal performance on the digit-span subtest, a task that is often considered a measure of immediate memory.

Table 1. Mean Performance of Alcoholic Korsakoffs and Nonalcoholic Controls on the WAIS<sup>1</sup>

	Korsakoffs	Controls
Age	53.4	53.2
Years of education	10.7	10.8
Full-scale WAIS	102.5	99.2
Verbal IQ	105.3	99.7
Performance IQ	98.5	97.2
Information	10.6	10.5
Comprehension	11.5	9.0
Arithmetic	9.6	9.5
Similarities	10.5	9.4
Digit span	9.4	8.7
Vocabulary	10.7	9.7
Digit symbol	3.4	6.8
Picture completion	9.5	9.7
Block design	8.2	7.7
Picture arrangement	7.7	7.7
Object assembly	8.6	6.5

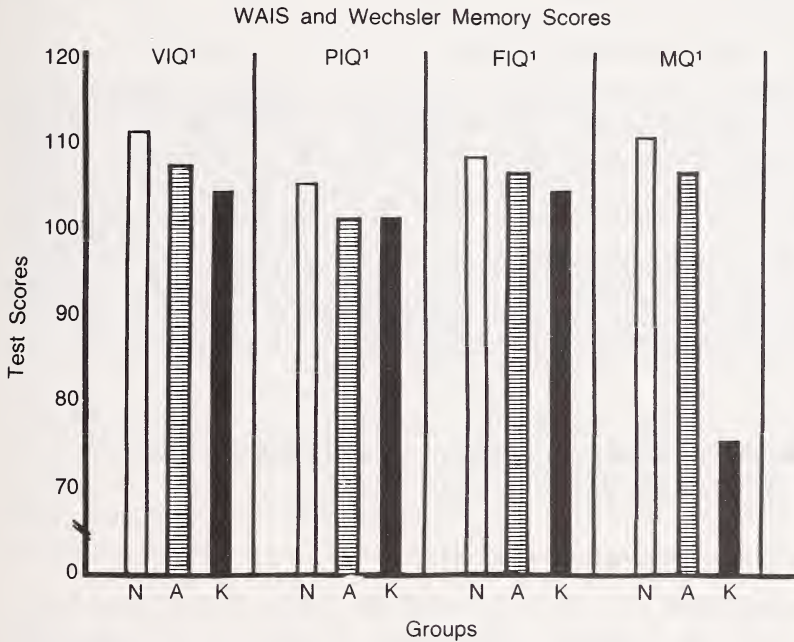
SOURCE: Reprinted with permission from *Empirical Studies of Alcoholism*, Copyright, 1976 Ballinger Publishing Company.

<sup>1</sup> Figures are rounded off to one place after decimal point.

Figure 1 shows the verbal IQ, performance IQ, full-scale IQ, and memory quotient (MQ based on the Wechsler Memory Scale) of nine alcoholic Korsakoff patients, 47 long-term alcoholics (non-Korsakoff), and 28 normal controls. Again, there are no differences between the Korsakoff patients and the other two groups on the IQ scores, although the MQs of the Korsakoffs are clearly impaired. This 20-30 point scatter between IQ and MQ is the psychometric hallmark of the amnesic

syndrome of alcoholic Korsakoff patients (Butters and Cermak 1976, 1980).

Figure 1. IQ and MQ Scores of Normal Controls (N), Chronic Alcoholics (A), and Alcoholic Korsakoff Patients (K)



SOURCE: Reproduced from Butters et al. 1977 with permission from the authors and the publisher. Copyright 1977 by Grune and Stratton, Inc.

<sup>1</sup> VIQ = verbal IQ; PIQ = performance IQ; FIQ = full-scale IQ; MQ = memory quotient.  
*Visuoperceptual Capacities*

Despite the normal IQs of alcoholic Korsakoff patients, their cognitive performance is not completely intact. A full neuropsychological evaluation usually reveals a number of secondary defects that may or may not contribute to their severe memory problems. The most common deficits involve visuoperceptive and visuospatial capacities. Alcoholic Korsakoffs are dramatically impaired on digit-symbol and symbol-digit substitution tasks (Glosser et al. 1977; Talland 1965), on hidden or embedded figures tests (Glosser et al. 1977; Kapur and Butters 1977; Talland 1965), and on various tests that require the sorting and discrimination of complex visual stimuli (Oscar-Berman 1973; Oscar-Berman and Samuels 1977). Such visuoperceptive deficits should not

be surprising, since chronic alcoholics who are not clinically amnesic have been reported to have the same perceptual problems (Goldstein and Shelly 1971; Goodwin and Hill 1975; Kleinknecht and Goldstein 1972; Parsons 1975; Parsons et al. 1971). Although there are some indications that these visuoperceptive deficits, like the patients' memory disorders, may be due to atrophy of limbic structures surrounding the third ventricle (Jarho 1973), many investigators have attributed these perceptual disorders to atrophy of cortical association areas (Parsons 1975; Parsons et al. 1971).

### *Olfactory and Gustatory Senses*

In addition to their visuoperceptive and conceptual deficits, Jones and her collaborators (Jones, Moskowitz, and Butters 1975; Jones, Moskowitz, Butters, and Glosser 1975; Jones et al. 1978) have reported that alcoholic Korsakoff patients are significantly impaired in their basic olfactory and gustatory senses. For both smell and taste stimuli, the Korsakoff patients have heightened intensity thresholds and noticeable difficulty in making qualitative discriminations. The investigators attribute these sensory deficits to the atrophy of several diencephalic structures anatomically associated with the olfactory and gustatory systems.

## ***Personality Characteristics of Alcoholic Patients With Korsakoff's Syndrome***

### *Motivational-Affective Characteristics*

No description of alcoholic Korsakoffs' major psychological symptoms would be complete without some mention of their *personality changes*. The Korsakoff patients often have premorbid histories of psychopathic behavior characterized by impulsive aggressive acts and petty crimes designed to support their chronic alcoholism. Many were "barroom brawlers" who also violently attacked members of their immediate families. With the onset of Korsakoff's disease, however, a dramatic change occurs in these motivational-affective characteristics. Instead of impulsivity, aggression, and severe alcohol abuse, the most prominent features are apathy, passivity, lack of initiative, and virtual disinterest in alcohol. The patients are also unable to formulate or organize a series of plans. Left to his own devices, a Korsakoff patient is likely to remain seated before a television set or even in bed for long periods of time, make few demands or inquiries of hospital staff, and obey all instructions in a passive but indifferent manner. The apathy of Korsakoff patients is not the consequence of institutionalization; this personality change is apparent shortly after they enter the Korsakoff phase of the illness and occurs even in patients who return to their home environments.



### *The Relationship Between Personality Changes and Cognitive Deficits*

One of the most perplexing and least investigated questions raised by the study of alcoholic Korsakoff patients concerns the relationship between their personality changes and their cognitive deficits. Talland (1965) has proposed that the Korsakoffs' difficulties in memory and perception are due to a faulty organization of cognitive strategies (i.e., a perseveration or rigidity of cognitive sets) resulting from a premature closure of activating mechanisms. That is, the patients' motivational and arousal deficits prevent a thorough coding of new information (anterograde amnesia) and the organization of suitable search strategies for scanning stored information (retrograde amnesia). Since it is commonly believed that arousal and attentional processes are dependent upon the reticular activating system (RAS), Talland assumed that the Korsakoff's midline diencephalic lesions interrupted the RAS's positive influence on cognitive (i.e., cortical) functions.

Granted that attentional factors may be responsible for some of the alcoholic Korsakoff's cognitive problems, it remains unlikely that most of the patient's amnesia can be explained by such concepts. Patients with frontal lobe lesions, including those who have undergone frontal lobotomies, also develop personality characteristics similar to those of Korsakoff patients, yet fail to evidence the striking amnesic symptoms. If impairments in activation can occur without a concomitant change in memory functions, some skepticism must remain as to the extent to which personality change influences the cognitive performance of Korsakoff patients.

### ***Neuropathology of the Wernicke-Korsakoff Syndrome***

There have been several recent reviews of the neuropathology of the Wernicke-Korsakoff syndrome (Brierly 1977; Mair et al. 1979; Victor et al. 1971), and only their major findings and conclusions will be outlined in this report. As Brierly (1977) notes, most of the literature supports the conclusion that the neurological symptoms of Wernicke's encephalopathy are related to lesions of the brain stem and cerebellum, while the amnesic symptoms of the chronic Korsakoff state involve damage to several thalamic and hypothalamic structures surrounding the third ventricle of the brain. The dorsomedial nucleus of the thalamus and the mammillary bodies of the hypothalamus are the specific structures most often associated with the alcoholic Korsakoff's amnesic symptoms.

Gamper (1928) studied the brains of 16 alcoholic Korsakoff patients and found that their lesions extended from the thalamus to the lower brainstem. He noted much variation from case to case, but concluded that the mammillary bodies were the crucial structure since all 16

Korsakoff patients had extensive atrophy of these nuclei. No correlations between brain pathology and clinical symptoms were reported.

Riggs and Boles (1944) examined the brains of 29 patients who had "Wernicke's disease." While alcohol abuse was associated with nearly one-half of these cases, the remaining cases were due to a number of other causes (e.g., prolonged vomiting). The neuropathological findings showed that the mammillary bodies were affected in 21 of 23 cases, the dorsomedial nucleus of the thalamus in 23 of 27, and the pulvinar of the thalamus in 10 of 14.

Delay et al. (1958a, b) described the neuropathology of eight alcoholic Korsakoff patients with both anterograde and retrograde memory deficits. Atrophy of the mammillary bodies was common to all cases, but significant thalamic involvement was noted in only one brain. These investigators stressed the lack of consistent cortical pathology, and pointed to the mammillary bodies as the most probable source of the patients' amnesic symptoms.

Adams et al. (1962) combined neuropathological findings with careful clinical and psychometric examinations of 300 Wernicke-Korsakoff patients. They found that the onset of the Wernicke stage was acute and subsided rapidly with the administration of large doses of thiamine. As the confusion, ataxia, nystagmus, and ocular palsies cleared, the patients' major remaining symptoms were severe anterograde and retrograde amnesia. Of the 300 cases, 54 brains were eventually studied. The investigators attributed the symptoms of Wernicke's disease to lesions in the brainstem (e.g., oculomotor nucleus) and cerebellum. The severe memory disorder of the Korsakoff stage of the illness was correlated with the presence of lesions in the mammillary bodies and several thalamic nuclei (dorsomedial, anteroventral, and pulvinar).

In a more recent report, Victor et al. (1971) examined the brains of 82 Wernicke-Korsakoff patients who had been carefully studied in terms of clinical symptomatology. Central to the issue of the neuroanatomical basis of the patients' amnesia were the results for the dorsomedial nucleus of the thalamus, which was examined in 43 of these brains. In 38 of the 43 brains, extensive atrophy of the dorsomedial nucleus was noted, but in the 5 brains with no atrophy there had been no lasting memory disorder. Since all 5 of these "negative" cases (as well as the 38 remaining cases) showed severe atrophy of the mammillary bodies, Victor et al. concluded that the dorsomedial nucleus, and not the mammillary bodies, is the critical structure for the amnesic syndrome. It should be noted, however, that another interpretation can be drawn from the presented data. Since all 38 cases with amnesia had lesions in both the mammillary bodies and the dorsomedial nucleus of the thalamus, it is possible that this combined thalamic-hypothalamic lesion is the one that is both necessary and sufficient for Korsakoff's amnesia. To demonstrate the primacy of the dorsomedial nucleus, it would be necessary to have amnesic cases with atrophy limited to the dorsomedial nucleus. Victor et al. did not report any cases meeting this criterion.

Based on the results of a recent neurochemical study (McEntee and Mair 1978), it appears possible that the Korsakoffs' diencephalic lesions are disrupting specific neural pathways that depend on monoamine-containing neurons. These investigators demonstrated that the cerebrospinal fluids of nine Korsakoff patients were significantly deficient in MHPG, the primary monoamine metabolite of norepinephrine. They also noted a significant correlation between the severity of the patients' memory impairment and their levels of MHPG in the cerebrospinal fluid.

Further evidence linking damage to norepinephrine-containing neurons in subcortical centers with patients' memory disorders was provided in a second study by McEntee and Mair (1980). In this investigation, several drugs that facilitate central norepinephrine activity were administered to eight patients with Korsakoff's disease. Each patient was examined on a neuropsychological test battery, which included measures of memory and of perceptual and conceptual functions, before and after 2 weeks of drug administration. The results showed that the administration of one drug, clonidine, was associated with significant improvements in several measures (e.g., Peterson short-term memory test, specific subtests of the Wechsler Memory Scale) of anterograde memory functions. If these results are confirmed in future studies, they suggest that therapeutic strategies aimed at increasing norepinephrine levels in the brain may help reduce the Korsakoff patients' amnesic symptoms.

## ***Etiology of the Wernicke-Korsakoff Syndrome***

### *Thiamine Deficiency*

Despite the evidence that Wernicke-Korsakoff's syndrome is related to specific subcortical lesions, the etiology of this brain damage remains obscure. Victor, Adams, and their colleagues (Brierly 1977; Dreyfus 1974; Victor et al. 1971) have gathered considerable data that point to thiamine (vitamin B1) deficiency as the primary factor in this disease. Since chronic alcoholics often fail to eat nutritionally balanced diets, malnutrition and avitaminosis are common correlates of chronic alcohol abuse. According to this nutritional theory, the diencephalon, the brainstem, and the cerebellum are very sensitive to thiamine deficiencies and either atrophy or become prone to hemorrhagic lesions.

Three principal forms of evidence support this theory of avitaminosis. First, the symptoms of Wernicke's stage occur commonly in disorders that interfere with food metabolism and absorption. Protracted vomiting during pregnancy, carcinoma of the stomach, chronic gastritis, and intestinal obstruction are some of the disorders associated with both malnutrition and the previously described Wernicke's symptoms.

Second, treating Wernicke-Korsakoff patients with large amounts of thiamine alleviates some of their symptoms. Ophthalmoplegia and the confusional state begin to improve within a few hours after the



administration of thiamine and usually clear within 7 days. The patients' nystagmus and ataxia show a slower and more limited improvement, and these symptoms may still be apparent in a mild form months or even years after the beginning of treatment. Of the various symptoms comprising the Wernicke-Korsakoff syndrome, the memory and personality changes remain the most resistant to thiamine therapy. Eighty percent of all Korsakoff patients show little, if any, improvement in their memory disorder and general apathy despite prolonged administration of vitamins. In fact, the amnesic disorder remains the chronic lifelong disability of alcoholic Korsakoff patients. Victor et al. (1971) believe that this marked variability in the reversibility of symptoms with vitamin therapy reflects differences in the stages of pathology. They conclude that symptoms associated with the Wernicke stage are reversible because they are due to a "biochemical abnormality that has stopped short of significant structural change," while the memory disorders of the Korsakoff stage of the illness are irreversible because of the presence of permanent structural damage (Victor et al. 1971).

The third form of support for the thiamine hypothesis stems from experimental studies in which animals have been deprived of thiamine for varying periods of time. While these studies have employed a wide range of animals, including man, monkeys, and rats, the overall results indicate that the major neurological symptoms of Wernicke's syndrome are associated with thiamine deficiency and that these symptoms are alleviated with the administration of thiamine (Brierly 1977; Dreyfus 1974; Mesulam et al. 1977; Victor et al. 1971). Monkeys, cats, and rats maintained on thiamine deficient diets usually develop diffuse lesions of the diencephalon, brain stem, cerebellum, and in some cases the basal ganglia. However, it is important to note that none of these experimental studies have shown that thiamine deficiency leads to chronic irreversible memory problems.

Blass and Gibson (1977) have presented some preliminary evidence that the Wernicke-Korsakoff syndrome develops only in those patients with a particular genetic metabolic abnormality. These authors studied the thiamine-requiring enzyme transketolase in four patients with the Wernicke-Korsakoff syndrome. The results indicated that transketolase from these patients was deficient in the binding of thiamine pyrophosphate. Since the abnormality in transketolase was apparent in cells grown in a medium containing excess thiamine and no ethanol, the investigators concluded that the deficiency had a genetic rather than a dietary origin. An exact mechanism by which deficiencies in transketolase might result in atrophy of the specific brain structures associated with Korsakoff's syndrome was not postulated.

### *Direct Toxic Effects of Alcohol on the Brain*

Although most textbooks of neurology accept avitaminosis as the primary cause of the Wernicke-Korsakoff disorder, there is now impressive data that prolonged alcohol ingestion, unaccompanied by

malnutrition, does result in permanent learning deficits and in significant brain pathology. Freund and his colleagues (Freund 1970; Freund and Walker 1971; Walker and Freund 1971; Walker and Hunter 1978) fed mice ethanol-containing liquid diets that were nutritionally controlled. After several months of this ethanol diet the mice were transferred to normal, ethanol-free laboratory diets for 2 months before the start of behavioral testing. Although these mice had never been fed a nutritionally unbalanced diet, they were impaired on a variety of behavioral tasks including avoidance and maze learning. In a recent study, Riley and Walker (1978) have reported that mice maintained for 4 months on Freund's ethanol liquid diet show a significant loss of dendritic spines on hippocampal pyramidal cells and dentate granule cells. The hippocampus, like the mammillary bodies and the dorsomedial nucleus of the thalamus, is a part of the limbic circuit concerned with memory processes.

This evidence that ethanol may have a direct toxic effect upon the brain suggests some reevaluations of the etiology of the Wernicke-Korsakoff syndrome. It is evident from our brief review that Wernicke's encephalopathy is closely linked to thiamine deficiency. Ocular palsies, nystagmus, and ataxia can be induced and then alleviated by controlling thiamine levels, and Victor et al.'s (1971) conclusion that these symptoms reflect brain stem and cerebellar abnormalities seems well supported by the experimental literature. The major controversy concerning etiology focuses upon the amnesic symptoms and the Korsakoff stage of the syndrome. Amnesic symptoms do not disappear with the administration of thiamine, and as Freund (1973) has noted, there is virtually no documented evidence of a *permanent* memory disorder in patients with thiamine deficiencies unaccompanied by alcohol abuse. In other words, thiamine deficiency appears to result in an amnesic syndrome only in alcoholic Korsakoff patients! It is possible then that the amnesic syndrome of the Korsakoff stage may result from an interaction of thiamine deficiency and the direct neurotoxic effects of alcohol. If this interaction hypothesis is valid, one would not necessarily expect a rapid onset of amnesic symptoms. Rather, the patients' difficulties in learning new materials should slowly become more prominent over the course of many years of alcohol abuse. In the next section of this report we shall review some recent data demonstrating such memory disorders in chronic, non-Korsakoff alcoholics.

### ***Continuities Between Detoxified Long-Term Alcoholics And Alcoholic Patients with Korsakoff's Syndrome***

Korsakoff's syndrome has traditionally been considered an illness of acute onset (Victor et al. 1971). The syndrome has been linked to a thiamine deficiency that results from alcoholics' poor dietary habits.



Since this thesis was discussed in the previous section, only a reminder that the etiology of this syndrome may be more complex than implied by the thiamine hypothesis is necessary here. The recent evidence suggesting that alcohol has a direct toxic effect on brain tissue (Freund 1973; Riley and Walker 1978) forces us to consider the possibility that Korsakoff's syndrome may be a chronic illness correlated with degree and length of alcohol abuse. Ryback (1971) has proposed such a continuity hypothesis and suggested that the alcoholic Korsakoff, the chronic alcoholic, and the heavy social drinker represent separate points along a single scale of cognitive impairment. Parker and Noble's (1977) demonstration of information processing deficits in social drinkers is certainly consistent with this thesis.

Continuities between alcoholic Korsakoff patients and detoxified long-term non-Korsakoff alcoholics have been demonstrated in numerous neuropsychological investigations. When contrasted with nonalcoholic control subjects, both chronic alcoholics and alcoholic Korsakoff patients perform poorly on visuoperceptual tasks requiring digit-symbol substitutions or the identification of embedded figures, with the scores of the chronic alcoholics falling midway between those of the Korsakoffs and the nonalcoholic controls (Glosser et al. 1977; Kapur and Butters 1977). Similar continuities between alcoholic Korsakoffs and chronic alcoholics have been demonstrated with complex visual problem-solving tasks. Oscar-Berman (1973) reported that alcoholic Korsakoff patients are more impaired than alcoholics on Levine's hypothesis-testing task. She found that the performance of both groups was inferior to that of neurologically intact control subjects and patients with Broca's aphasia. Alcoholics also have been reported to be impaired on other visuoperceptual concept formation tasks, such as the Wisconsin Card Sorting Test (Tarter 1973; Tarter and Parsons 1971), the Halstead Category Test (Fitzhugh et al. 1965; Jones and Parsons 1971) and the Advanced Form of Raven's Progressive Matrices (Jones 1971). Kleinknecht and Goldstein (1972) and Goodwin and Hill (1975) have written extensive reviews documenting the chronic alcoholics' deficits on these various visuoperceptual and conceptual tasks.

Despite these demonstrations of a continuity between detoxified long-term alcoholics and alcoholic Korsakoff patients, the feature most characteristic of Korsakoff's syndrome is conspicuously absent from the neuropsychological analyses of chronic non-Korsakoff alcoholics. Almost without exception, investigators have been unable to demonstrate the presence of a significant, relatively stable memory defect in *detoxified* alcoholics (Parsons and Prigatano 1977).

There are at least two plausible explanations for the failure to find verbal memory deficits in detoxified chronic alcoholics. One is that a permanent memory deficit appears only when alcoholism is combined with a chronic thiamine deficiency. Victor et al. (1971) have shown that atrophy of structures surrounding the third ventricle (i.e., the dorsomedial nucleus of the thalamus and/or the mammillary bodies) is the common denominator in Korsakoff's syndrome, and have postulated



that thiamine deficiency is both necessary and sufficient to produce the syndrome. Since most chronic alcoholics may eat enough to maintain a sufficient level of thiamine, the short-term verbal memory deficits associated with diencephalic-limbic damage may be apparent in only a small percentage of chronic alcoholics.

A second possibility is that investigators have not utilized tests appropriate to gauging the alcoholics' verbal memory deficits. If the alcoholics' memory deficit is actually an attenuated form of the Korsakoffs' retention disorder, then only specific tasks of sufficient complexity should differentiate long-term chronic alcoholics from short-term alcoholics and nonalcoholic controls. Determining whether this latter hypothesis is valid has not only theoretical significance but also practical value in the diagnosis and evaluation of alcoholics.

The results of three recent studies suggest that chronic alcoholics and alcoholic Korsakoff patients do share qualitatively similar anterograde memory problems. In the initial study, Butters et al. (1977) administered a battery of short-term memory, encoding, and standardized psychometric (WAIS, WMS) tests to 62 detoxified alcoholics, 9 alcoholic Korsakoff patients, and 28 nonalcoholic controls. The 47 patients who had been alcoholics for 10 or more years were designated as the long-term alcoholic group (LTA). The remaining 15 alcoholics had all abused alcohol for less than 10 years and were designated as the short-term alcoholic group (STA). The LTA, STA, and nonalcoholic control groups were matched for age (mean: 43 years) and educational background.

The results of the initial study were disappointing. While deficits on the visuoperceptual tasks (e.g., the digit-symbol subtest of the WAIS) were clearly related to years of alcohol abuse, none of the short-term memory and information processing tasks yielded significant differences among the two alcoholic groups and the normal controls. In evaluating these negative findings the problem of test complexity was considered. It is well known that if neuropsychological tests are made too difficult, all brain-damaged patients may fail them, and the utility of the tests for making differential diagnosis may be reduced. On the other hand, if the tests are too easy, only patients with severe impairments may be identified, and patients with mild-to-moderate deficits may appear normal. The latter situation seemed most applicable to the Butters et al. (1977) study. That is, memory tests that were designed to assess the learning and retention deficits of amnesic Korsakoff patients may have been too simple to detect moderate but progressive impairments in long-term alcoholics.

To assess the possibility that the simplicity of the tests had been masking the deficits of non-Korsakoff alcoholics, Ryan et al. (1980) administered a new and more complex battery of memory tasks to 18 detoxified long-term alcoholics, 28 nonalcoholic controls, and 7 alcoholic Korsakoff patients. The mean age of all three groups was between 53 and 55 years. Two of the redesigned tests involved paired-associate learning and one a short-term memory paradigm. One of the paired-

associate tasks required the patients to learn to associate single-digit numbers with unfamiliar geometric patterns; the other paired-associate task involved the association of two words of relatively low association value. The short-term memory task was made difficult by presenting four words on each trial (instead of the word triads used in previous studies of Korsakoff and demented patients) and utilizing 30 seconds (rather than 18 seconds) as the maximum delay (distractor interval) between presentation and recall. To ensure that any noted memory deficits were related to alcohol rather than to secondary complications, stringent selection criteria were used for the alcoholic subjects. Any alcoholic with a history of ECT, severe head trauma, schizophrenia, polydrug abuse, cirrhosis, epilepsy, or childhood learning disabilities was excluded from the study. Despite these stringent criteria, the results of the investigation revealed severe memory deficits in the long-term alcoholics. On all three memory tasks, the performance of the detoxified alcoholics fell midway between the scores of the normal controls and the amnesic Korsakoff patients. It was also found that the alcoholics, like the Korsakoff patients, did not utilize the mnemonic strategies employed by the normal controls on the paired-associate tasks.

A second study (Ryan and Butters 1980a) using this redesigned memory battery addressed two additional questions. One, are memory deficits apparent in young as well as middle-aged alcoholics with equivalent drinking histories? Some studies (Jones and Parsons 1971; Klisz and Parsons 1977) have suggested that conceptual deficits are prevalent only in long-term alcoholics over 50 years of age, but the role of age in the development of memory deficits has not been investigated. Two, are the memory deficits of alcoholics consistent with the premature aging hypothesis? It has been noted that the neuroanatomical and cognitive changes associated with alcohol abuse are also characteristic of the normal aging process (Kleinknecht and Goldstein 1972), a parallel that implicates alcohol as an agent that may accelerate aging.

To assess these issues the complex paired-associate and short-term memory tests were administered to five groups of subjects: young alcoholics (34-49 years), middle-aged alcoholics (50-59 years), young normal (nonalcoholic) controls (34-49 years), middle-aged normal controls (50-59 years), and elderly normal controls (60-65 years). All alcoholics had been detoxified for at least four weeks, and the same selection criteria detailed in the previous investigations were again used. The young and middle-aged alcoholics were carefully matched for the length of their drinking history (mean: 20 years).

The results of this investigation indicate that young as well as middle-aged long-term alcoholics are impaired in their ability to learn and retain new materials, and the data also provide support for the premature aging hypothesis. On all three memory tests, young and middle-aged alcoholics were significantly impaired in comparison to their respective controls, but performed almost identically to one of the older control groups. Thus, the performance of the young alcoholics was impaired in

comparison to that of the young controls, but did not differ from the performance of the middle-aged controls. Similarly, the middle-aged alcoholics were impaired in comparison to middle-aged controls, but had scores that approximated those of the elderly controls.

A third study (Ryan and Butters 1980*b*) utilizing the redesigned memory battery was concerned with the differentiation of various alcoholic populations along Ryback's (1971) proposed continuum of cognitive impairment. Long-term detoxified alcoholics who met the described stringent selection criteria were divided into two groups based on the presence or absence of memory complaints. Each alcoholic was given a structured interview during which he was questioned concerning his ability to learn new materials and to recall past events. Alcoholics who complained of a significant deterioration in their memory capacities were placed in one group while alcoholics who had not noted any slippage in their retentive capacities were treated as a separate group. None of the alcoholics in either group had a history of Wernicke's encephalopathy or manifested Korsakoff symptomatology on a mental status examination. Because Ryback's continuity hypothesis implies the existence of a number of intermediate degrees of impairment, it was expected that the test performance of alcoholics with memory complaints would be impaired relative to alcoholics without such complaints. The results were consistent with this prediction. While both alcoholic groups were impaired in comparison to the controls on the paired-associate and short-term memory tasks, the alcoholics with memory complaints performed significantly worse than did alcoholics without memory complaints. In a number of instances, the learning and retention scores of the alcoholics with memory complaints and of true alcoholic Korsakoff patients were indistinguishable. These findings, like those of the two previous studies reviewed, offer substantial support for the continuity hypothesis and indicate that at least some of the memory deficits of alcoholic Korsakoff patients may develop slowly during years of alcohol abuse.

These demonstrations of anterograde memory deficits in long-term (non-Korsakoff) alcoholics appear to offer a possible explanation for the specific characteristics of the alcoholic Korsakoff patient's retrograde amnesia (i.e., inability to recall events that occurred before the onset of the illness). The Korsakoff patient's impairment in recalling past events is severe, involves several decades of life, and is characterized by a steep temporal gradient in which memories from the patient's childhood and young adulthood are better preserved than those from the years just prior to his illness (Albert et al. 1979). One possible explanation for this temporal gradient is that the retrograde amnesia may not have an acute onset but may reflect a progressive deterioration of the patient's ability to learn new information. If, as Ryan and Butters' results suggest, the chronic alcoholic acquires less information each year due to an increasing deficit in information processing, then at the time the patient is finally diagnosed as an "alcoholic Korsakoff," one would expect to find a retrograde amnesia with a temporal gradient. From this viewpoint,



the alcoholic Korsakoff patient's retrograde amnesia might be considered secondary to a primary defect in establishing new memories during his years of alcohol abuse.

To assess this "chronic" interpretation of the Korsakoff's retrograde memory problems, several tests of retrograde amnesia were administered to long-term detoxified alcoholics (Albert, Butters, and Brandt 1980; Albert, Butters, and Levin 1980). It was hypothesized that if the "chronic" interpretation is valid, long-term alcoholics should demonstrate significant deficits in their recall of past public events and famous people, and that these impairments should be more severe for the immediately preceding years (the 1970s) than for the early years of the patient's alcoholic history (1940s and 1950s). In both studies, the Boston Retrograde Amnesia Test Battery (Albert et al. 1979) was used to evaluate remote memory.

The results of both investigations uncovered only mild remote memory deficiencies in long-term alcoholics. On the face identification and multiple-choice questionnaire, no significant differences were found between the alcoholics and their nonalcoholic controls on "easy" or "hard" items regardless of the presence or absence of cues to facilitate recall. On the recall test, a significant difference was noted under a single condition: when no cues were available, the alcoholics were moderately impaired in their recall of "hard" items from the 1970s and 1960s, but continued to demonstrate normal recall for the 1930s, 1940s, and 1950s.

The findings of the 1980 studies by Albert and her colleagues offer some evidence of a remote memory problem in chronic alcoholics, but they certainly do not provide strong support for the hypothesis that the Korsakoff patients' retrograde amnesia can be totally explained by a preexisting deficit in acquiring new information. The remote memory problems of alcoholics seem subtle and are evident only under the most taxing of recall conditions (no cues, hard items). If the Korsakoff patients' retrograde amnesia was primarily due to a chronic and progressive deficit in new learning, the long-term alcoholics should have had far more pervasive and severe deficits on Albert et al.'s test battery.

Although the results of the 1980 studies do not permit reduction of the Korsakoff patients' retrograde amnesia to an anterograde problem, they do suggest that two separate etiological factors may be involved. One factor is the impact of chronic alcohol abuse on anterograde memory processes. Since long-term alcoholics may retain somewhat less information each year due to a chronic learning deficit, their store of remote memories for the recent past may be mildly or moderately deficient. The second factor may be a forgetting of old memories that appears acutely during the Wernicke stage of the illness and results in a severe and equal loss for all time periods prior to the onset of the disease. When this acute loss of remote memories is superimposed on the patients' already deficient store, a severe retrograde amnesia with a temporal gradient would be expected. Patients should be impaired with respect to controls at all times, but memory for recent events should be

most severely affected since less had been learned initially during this period.

The results of these remote memory studies also suggest that anterograde and retrograde amnesia can be dissociated from one another and may involve different neural circuits. Although alcoholic Korsakoff patients clearly demonstrate both types of amnesia, non-Korsakoff alcoholics have substantial difficulty learning new information, but are often only mildly impaired in their recall of remote events. The fact that alcoholic Korsakoff and postencephalitic patients show a double dissociation on specific tests of new learning (Butters and Cermak 1976) and on Albert et al.'s tests of remote memory (Butters 1979) lends further support to the separability of anterograde and retrograde memory problems.

It is not possible at this juncture to determine the exact neural circuits that mediate anterograde and retrograde memory processes, but a report based on stimulation studies with epileptic patients (Fedio and Van Buren 1974) has produced evidence for such an anatomical separation within the temporal lobes. Since the amnesia of alcoholic Korsakoff patients is often attributed to damage to the dorsomedial nucleus of the thalamus and to the mammillary bodies (Victor et al. 1971), it is also of interest that the patient (Teuber et al. 1968) who is severely amnesic with regard to the learning of new verbal material, but has a very mild retrograde amnesia, has now been reported (Squire and Moore 1979) to have unilateral destruction of the dorsomedial nucleus and no other visible damage. Perhaps the alcoholic Korsakoff patients' severe anterograde amnesia develops slowly due to the gradual atrophy of the dorsomedial nucleus while their loss of remote memories appears suddenly with acute damage to other subcortical brain structures.

In addition to studies of the memory disorders of alcoholics, the continuity issue has been evaluated with regard to sensory functions. Several studies (Jones, Moskowitz, and Butters 1975; Jones, Moskowitz, Butters, and Glosser 1975; Jones et al. 1978) have demonstrated that patients with alcoholic Korsakoff's syndrome have severe deficits in olfactory and gustatory abilities. Korsakoff patients are impaired in the psychophysical scaling of odor and gustatory intensities and have difficulty making odor quality discriminations. Despite the consistency with which these sensory deficits have been noted in Korsakoff patients, there has been little evidence that long-term (non-Korsakoff) alcoholics have undergone any significant changes in their smell and taste capacities. Jones and her colleagues employed both alcoholic and nonalcoholic controls in all three of these investigations, but failed to uncover significant differences between these two groups.

There are at least two reasons why these studies may have failed to note olfactory deficits in chronic alcoholics. One, the neuropathology which disrupts the capacity for appreciating odor and odor quality may not be characteristic of alcoholics, but may develop acutely with the onset of the Wernicke-Korsakoff disorder. Two, the failure of Jones et

al. to detect olfactory impairments among long-term alcoholics may be due to the fact that their olfactory tests were relatively simple and easily mastered by patients with subtle forms of neuropathology. To test this second possibility, Potter and Butters (1980) designed a new battery of olfactory tests (odor detection, odor quality discrimination) which were more sensitive and difficult than those used by Jones and associates. The psychophysical technique of signal detection (a method that provides a more accurate measure of absolute sensitivity than traditional procedures), less intense olfactory stimuli, and more closely matched odor pairs were employed in these new discrimination tasks.

The results with this new and more complex sensory battery indicated that long-term (non-Korsakoff) alcoholics do in fact have olfactory deficits. The alcoholic Korsakoffs were again severely impaired (i.e., chance performance) on both the odor identification and odor quality scaling tasks, and the alcoholics' performance on both olfactory tasks fell midway between scores of the Korsakoff patients and nonalcoholic controls. On a complex hue discrimination task the three groups were indistinguishable, a finding that underlines the modality-specific nature of the alcoholics' sensory loss.

In summary, investigations of the past 3 years have demonstrated that some of the symptoms that characterize alcoholic Korsakoff's syndrome are evident in an attenuated form in detoxified long-term alcoholics. Like the Korsakoff patient, the long-term alcoholic is impaired on visuoperceptual-conceptual tasks, has difficulty acquiring new information, and has lost some of his olfactory sensory capacity. It appears then that Korsakoff's syndrome may not be as acute as once believed, but may develop in a slow progressive manner during many years of alcohol abuse. The present findings do not, however, necessarily imply that the neurotoxicity of alcohol is totally responsible for the patients' neurobehavioral problems. Both malnutrition and the interaction between malnutrition and the toxic effects of alcohol may contribute to the neuropathology and the resulting behavioral deficits associated with long-term alcohol abuse.

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## **Chapter 9**



# Alcohol as a Teratogen in Animals

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## Abstract

While alcohol has been considered for nearly 200 years to have teratogenic potential, it is only recently that the Fetal Alcohol Syndrome (FAS) was named to refer to a specific pattern of malformations common to the offspring of chronic alcoholic women. This constellation of defects includes prenatal and postnatal growth deficiencies, central nervous system anomalies, craniofacial peculiarities, and associated major and minor malformations. The evidence from both the clinical and animal literature indicates that alcohol indeed is a teratogen in its own right. Animal studies have served to clarify the role of prenatal alcohol exposure in the etiology of birth defects, since they have produced a pattern of malformations bearing a striking similarity to FAS, in the presence of carefully controlled nutritional and environmental factors. The results of the animal studies on growth and development parallel those of the human studies, reporting that retarded prenatal growth, increased prenatal mortality, and higher incidence of morphological anomalies are directly related to the amount of alcohol consumed by the mother, but suggesting that genetic background may be an important factor. While human research reports that mental retardation and delayed psychomotor development are primary features of FAS, the neuroanatomical work has given insight to possible underlying structural brain anomalies and has indicated that brain maturation is retarded as well. Unfortunately, the few neurochemical and biochemical studies conducted to date have been unable to report conclusive results. It is to be expected that research dealing with alcohol-induced teratogenesis will be increased in the future, since current work has generated many hypotheses and many clinical issues concerning FAS need to be addressed. For example, critical periods and doses need to be defined, the contribution of maternal drinking prior to pregnancy clarified, and the role of paternal alcohol consumption in producing birth defects evaluated. Finally, the specific mechanism by which alcohol acts to affect fetal development remains to be elucidated.



## ***Introduction***

Teratology, the science of congenital malformations, has a long history dating back to the early 1800s. The pioneer teratology experiments were performed in nonmammalian species. These early studies demonstrated that the normal course of avian and amphibian development could be altered by environmental or chemical insult. Although the results from nonmammalian studies were convincing, they were considered to have little relevance to mammals, especially humans. This is not to say that the medical-scientific world was not interested in malformation or that it did not recognize the occurrence of abnormal development. Rather, malformations were attributed to genetic factors. It was thought that the developing mammalian fetus was protected from harm by the mother and that *in utero* insult had minimal effect on the course of development (Warkany 1965).

A growing body of experimental literature in laboratory mammals in the first few decades of the 20th century emphasized to researchers and medical professionals that environmental events like hypoxia and x-irradiation, specific vitamin deficiencies, and maternally administered drugs were, in fact, capable of producing anomalous development (Warkany 1965). The thalidomide tragedy in the 1960s demonstrated that humans also were not immune to teratologic influences. This event served to rekindle recent medical and scientific interest in the field of teratology (Warkany 1979). The continual recognition of additional teratogenic agents, especially drugs (Wilson 1972), has maintained this interest. Animal research to screen and study potential teratogens has become recognized as an important adjunct to clinical observations.

It should be noted that the definition of teratology has been broadened from the classical one of grossly observable anomalies that are recognized at birth to a definition that includes structural as well as functional and biochemical anomalies that can occur at birth or many years later. This state-of-the-art review utilizes the current broad definition.

The focus of this article is on the teratogenicity of alcohol in animals. It briefly summarizes the pioneer studies in this area, moves on to the results that have been reported since 1973 on the effects of prenatal alcohol exposure on growth, development, biochemistry, and brain function, and ends with a critical evaluation of the data and future trends in the field.

## ***Alcohol as a Teratogen: Brief Historical Perspective***

### ***Nonmammalian Species***

Interest in alcohol and embryonic development paralleled the development of the science of teratology as a whole. That is, the earliest experiments were performed in nonmammalian species (Ran-

dall and Noble 1980). Alcohol was a convenient agent to use because it is soluble in water and also is volatile, so it can be administered either in solution or as a vapor.

The chick embryo was a popular species to study. Exposure of incubating eggs to alcohol vapor for varying lengths of time resulted in a range of adverse effects from growth retardation and abnormal development to death (Stockard 1932). Direct treatment of the eggs of fish *Fundulus heteroclitus* with graded doses of alcohol in sea water also yielded a high incidence of abnormally developed embryos with increased mortality as alcohol dose increased (Stockard 1910). After several years of experimentation, Stockard (1932) concluded that the action of alcohol (as well as other anesthetics) on the embryo was to retard development, which in turn caused suppressed or abnormal development of the various parts of the body. Thus the type of abnormality induced was thought to be related to the specific developmental stage of the embryo and not to the nature of the agent. Several agents produced the same type of defect when given at identical developmental stages. This is an important point to keep in mind, for as Stockard (1932) states, 'There can be no specific action for alcohol on the embryo. If effective, alcohol acts as other effective agents do to slow the rate of development.'

It has been argued that results from nonmammalian studies are of little significance to humans, because the concentrations of alcohol required to directly affect development were several times higher than is possible in humans (Randall and Noble 1980). However, the conclusions drawn from the experiments and the theories proposed to explain the results are of major importance to the field of teratology and to the understanding of the actions of alcohol on embryonic development in general.

### *Mammals*

In mammals, the only way alcohol can reach the fetus is through the mother's blood. For many years, it was thought that the placenta was impermeable to most substances, so it is understandable that research with mammals did not begin until after it was demonstrated in the early 1900s that alcohol could be measured in fetal tissues (Nicloux 1899).

Stockard (1932) performed the most systematic studies in the area using guinea pigs as subjects. Alcohol was administered to the animals as vapor. His results demonstrated that alcohol-treated parents produced smaller litters because of an increase in prenatal deaths. Birthweights, however, were comparable to controls, and only occasional reference was made to defective embryos. Increased prenatal mortality continued in subsequent generations until, in the fourth filial generation away from treatment, prenatal mortality was reduced and the surviving offspring were hardier than the control stock. Investigators utilizing other lab animals could not support Stockard's findings, however (Randall 1977). Possibly because of these inconsistent

findings or the era of Prohibition, interest in the effects of alcohol on prenatal development waned.

It is difficult to draw conclusions about the teratogenicity of alcohol from the early studies. While it is true that researchers who employed nonmammalian species were interested in the teratogenicity of alcohol, the focus is not as clear in the mammalian literature. For example, the experiments were not designed to answer the question of whether alcohol was a teratogen. In many cases, both male and female parents were treated, and females were treated with alcohol prior to conception as well as during pregnancy and lactation. Thus it is impossible to determine whether alcohol-related genetic damage in either parent (i.e., mutagenicity) or postnatal maternal variables induced by alcohol, such as alterations in maternal behavior or milk supply, were responsible for the observed effects, rather than prenatal exposure alone. Furthermore, the studies were plagued with other methodologic complications such as inadequate nutritional controls and variable duration of alcohol treatment, which weaken the significance of the studies even further. In summary, it is not clear from the pioneer studies in mammals that alcohol, per se, is a teratogen (Randall and Noble 1980).

## ***Alcohol as a Teratogen: 1973-1979***

### *The Fetal Alcohol Syndrome*

The report by Jones and colleagues (1973) recognizing a pattern of malformation in offspring of alcoholic women that included prenatal/postnatal growth disturbances, central nervous system anomalies, craniofacial peculiarities, and other associated major and minor defects rekindled scientific interest in alcohol as a teratogen in the United States and abroad. The constellation of defects was labeled the fetal alcohol syndrome (FAS) (Jones and Smith 1973). Two animal studies that demonstrated alcohol-induced dysmorphogenesis in the chicken (Sandor and Elias 1968) and the rat (Sandor and Amels 1971) were brought to the attention of the scientific community as support for the notion that alcohol was the teratogen that caused FAS, rather than nutritional or other confounding variables that are associated with alcohol abuse (Jones and Smith 1973). Since 1973, animal studies investigating the effects of prenatal alcohol exposure on development of the offspring have proliferated, some with the specific intention of developing an animal model of FAS (Chernoff 1977), and others more concerned with determining whether alcohol was in fact a teratogen as evidenced by its ability to alter morphologic development when administered during the period of organogenesis (Kronick 1976; Randall and Taylor 1979; Skosyreva 1973). However, regardless of the focus of the studies, the basic issue under investigation was the teratogenicity of alcohol in animals.



*Routes of Alcohol Administration and Species Employed in Animal Models*

Before going on to discuss the results of animal studies, it is necessary to briefly describe some of the background methodologies, especially those related to alcohol administration to animals, and to mention the different species that have been employed.

Today, the most common method of administering alcohol to laboratory rodents is in a liquid diet, which replaces the animals' solid chow and water. Alcohol in known concentrations is added to the commercially available liquid diet that has been fortified with additional vitamins, and the daily consumption is monitored to determine daily caloric and alcohol intake. Control animals are fed an identical liquid diet, except with isocaloric replacement of sucrose for the ethanol in the experimental diets. Each control animal receives the same volume of diet the experimental animal consumed the previous day. In this way, caloric intake is equated between groups. Undernourishment cannot be an explanation of the results if the pair-fed control group does not differ from the *ad libitum* chow group included in the design. This is not to say, however, that malabsorption from the gut or malassimilation of ingested nutrients is equated between the groups. This method of alcohol administration is convenient to the experimenter and nonstressful to the animal, the latter point being of primary concern in experiments employing pregnant animals.

Another popular route of administration used in some of the studies to be described in the following sections is the intragastric route. With this procedure, a known dose of alcohol is intubated directly into the stomach. Control animals are intubated with an equal volume of an isocaloric sucrose solution. In some studies, the amount of solid food consumed by the experimental animal is measured and fed to the control animal in order to equate daily caloric intake in the two groups. Ideally, a chow group is included for comparison. Once again, as with the liquid diet technique, there is emphasis on controlling for nutritional variables, but this procedure is more stressful to pregnant animals than the liquid diet technique, because of the required repeated handling of the animals. There is a large body of literature documenting the adverse effects of maternal stress on pregnancy outcome (Defries et al. 1967; Hockman 1961; Smith et al. 1971).

Two lesser used methods of alcohol administration are to replace the animal's water with a dilute alcohol solution or to inject the alcohol intraperitoneally. This latter method is not recommended for pregnant animals because of possible puncture of the fetus or sac.

Mice and rats have been utilized most frequently in recent studies in this area (Randall and Taylor 1979; Riley et al. 1979), and in animal teratology in general, but other animals that have been studied include the dog (Ellis et al. 1977), monkey (Jacobson et al. 1980), rabbit (Schwetz et al. 1978), miniature swine (Dexter et al. 1979), guinea pig (Papara-Nicholson and Telford 1957), and kitten (Himwich et al. 1977).

The remainder of this section summarizes the results of studies concerned with the effects of prenatal alcohol exposure on various aspects of offspring development.

### *Prenatal Alcohol: Effects on Growth and Development*

**Litter Size, Weight, Postnatal Mortality.** Litter size is frequently overlooked as a measure of teratogenesis, but it is an extremely powerful index, for it can be assumed that the fetuses most affected by a teratogen die *in utero* or are stillborn. Interestingly, the literature concerned with the effects of alcohol treatment during pregnancy on litter size at birth has not demonstrated a consistent decrease in the number of pups born to alcohol-treated mothers (Abel 1980). This is surprising in light of the fact that alcohol treatment has been reported to increase the number of prenatal deaths observed in mice (Chernoff 1977; Kronick 1976; Randall and Taylor 1979) and in rats (Skosyreva 1973), as evidenced by inspection of the uterus immediately before delivery.

With regard to birthweight, it appears safe to conclude that maternal alcohol treatment decreases weight in the progeny (Abel 1978; Abel and Dintcheff 1978; Ellis and Pick 1976; Ewart and Cutler 1979; Harris and Case 1979; Tze and Lee 1975; Volk 1977). The quantitative effect, however, seems to be related to treatment period (Abel 1979) and genotype (Yanai and Ginsburg 1977). More specifically, Abel (1979) reported that alcohol treatment of pregnant rats by intubation during the third trimester had a more severe effect on birthweight of the litter than did treatment earlier in gestation, while Yanai and Ginsburg (1977) observed a decrease in birthweight for alcohol-exposed DBA progeny but not for similarly exposed progeny of C57BL mice. Although the cause of alcohol-induced growth impairment has not been identified conclusively, the recent findings of Thadani and Schanberg (1979) in the rat suggest that a disturbance in growth hormones in alcohol-exposed pups may be a possible explanation. Other explanations await further experimentation. It should be noted, however, that growth hormone release in children with FAS has been reported to be normal (Root et al. 1975).

Just as prenatal mortality is an index of teratologic insult, so is postnatal mortality. Functional anomalies not observable at birth may become manifest as the organism matures. If the defect is serious enough, the organism will die. Interestingly, some investigators have reported an increase in postnatal mortality in progeny of alcohol-treated pregnant rats (Henderson and Schenker 1977; Martin et al. 1977) but, as Abel (1980) pointed out in his review of the literature, the confound of raising the progeny with their own mothers instead of being fostered to untreated mothers at birth makes it impossible to determine the cause of the increased postnatal mortality. Alcohol treatment may have

interfered with maternal behavior or more important, with the production of milk.

In summary, the most dramatic effect of prenatal alcohol exposure in animals on growth and development is a decrease in birthweight. The significance of this finding is that intrauterine growth retardation is also a major feature of FAS in humans.

### Morphologic Anomalies.

By definition, a teratogen is an agent that produces anomalous development, not only in growth patterns but in structural and functional development as well. Skeptics of FAS claimed that the congenital defects observed in the offspring of alcoholic mothers could have been caused by maternal malnutrition, vitamin deficiency, nicotine, infection, or a number of other adverse conditions that are frequently associated with alcohol abuse (Mendelson 1978), although several arguments for FAS' being a discrete entity have appeared in the clinical literature (Hanson et al. 1976). Still, clinical proponents of FAS turned to animal researchers to prove that alcohol was in fact a teratogen in its own right. The results from the animal studies strongly support the notion that alcohol is indeed a teratogen.

Despite the relatively few studies that have been done in this area and the dramatic differences in their methodology, the results from the studies were similar (Chernoff 1977; Ellis and Pick 1980; Kronick 1976; Randall et al. 1977; Randall and Taylor 1979). The consistent findings were that frequency of fetal death was higher in the offspring of alcohol-treated mothers, the incidence of structural anomalies was increased after maternal alcohol treatment, and the deleterious effects appeared to be dose related. It is also interesting to note that Chernoff (1977) and Randall and colleagues (1977) observed strain differences in susceptibility to the teratogenic effect of alcohol, which emphasizes the importance of genetic background.

The results from these studies are of utmost significance because they demonstrate the teratogenicity of alcohol in laboratory animals under controlled conditions and in the absence of confounding variables. Chernoff (1977), Randall and Taylor (1979), and Ellis and Pick (1980), for example, used a pair-fed nutritional control as well as an untreated group that had free access to food and water. The strength of this type of design is that malnutrition in the alcohol-treated group can be controlled for in the pair-fed group, and a comparison between the two control groups will demonstrate whether reduced maternal food intake, per se, is associated with an increase in birth defects. In the studies mentioned above, alcohol treatment, not reduced food intake, seemed to be the most important variable. However, it should be pointed out that it is impossible to rule out nutritional variables completely because there may be differences in absorption of essential nutrients from the gut in alcohol-treated mothers.



In addition to demonstrating that alcohol was teratogenic in animals, this body of literature also made another significant contribution to the FAS area. More specifically, the animal studies revealed a pattern of birth defects similar to those reported in FAS children (Clarren and Smith 1978). The defects observed in mice and dogs included hydrocephaly, cardiac anomalies, hydronephrosis, digit peculiarities, and cleft palate (Chernoff 1977; Ellis and Pick 1980; Randall and Taylor 1979). Interestingly, the renal anomalies were demonstrated in mice (Randall et al. 1977) prior to their inclusion as a feature of the FAS (DeBeukelaer et al. 1977), which emphasizes the importance of animal models of FAS.

It should be noted that in two studies (Schwetz et al. 1978; Skosyreva 1973) designed to investigate the teratogenic potential of alcohol in animals, teratogenic effects were not observed. The results of these studies may be explained by species or strain differences or other basic differences in methodology, but a more likely explanation is that the alcohol dose was too low to produce visibly defective offspring. Both Chernoff (1977) and Randall and Taylor (1979) emphasized the importance of dose and maternal blood alcohol level in the production of defective fetuses. Doses that produce blood alcohol levels less than 100 mg/dl have not been found to be teratogenic, at least with regard to morphologic defects.

In summary, animal studies in mice and dogs have demonstrated that alcohol is teratogenic in the presence of adequate maternal intake of nutrients and without other confounding variables. The effect, however, is dose related and is influenced by the genetic background of the animal. These conclusions from animal studies not only provide strong support for the existence of FAS, but they have potential clinical application as well.

### *Prenatal Alcohol: Effects on the Brain*

#### Neuroanatomical Changes

In the course of routine teratologic evaluation, Chernoff (1977), Randall and Taylor (1979), and Kronick (1976) observed brain anomalies in offspring of alcohol-treated mice. The defects included hydrocephalus (Chernoff 1977; Randall and Taylor 1979; Randall et al. 1977), exencephaly (Kronick 1976; Randall and Taylor 1979) and absent corpus callosum (Chernoff 1977). These findings of course represent gross neuroanatomical defects. Many of the primary features of FAS (Clarren and Smith 1978) such as mental retardation, delayed psychomotor development, and impaired fine motor coordination imply structural changes at a microscopic level as well. Researchers interested in using animal models of FAS to determine whether neuroanatomical defects occur at the cellular level have been faced with a serious problem. Unlike the human brain, the brain of the rat or mouse does not mature fully *in utero*. Thus alcohol exposure during *gestation* in these species is not a very good model to investigate human brain alterations.

Nevertheless, the model can supply some useful information if 'the models themselves are good. Unfortunately, the models employed in this area have been plagued with two major methodologic flaws. The first is the lack of a nutritional control group (Jacobsen et al. 1978; Majdecki et al. 1976; Volk 1977), and the second is the absence of fostering at birth (Druse and Hofteig 1977; Hofteig and Druse 1978; Jacobsen et al. 1978; Majdecki et al. 1976). The significance of the results is therefore weakened. However, the consistency of the findings suggests an effect of alcohol on brain development.

The results of the few studies reported follow a common theme. That is, brain development is retarded (Druse and Hofteig 1977; Hofteig and Druse 1978; Jacobson et al. 1978; Majdecki et al. 1976; Volk 1977) but catches up to controls with age (Jacobson et al. 1978; Volk 1977). Along the same theme, fetal brain cell number was reported to be reduced in near-term rat pups born to mothers fed 15 percent ethanol in water (Woodson and Ritchey 1979).

In summary, studies in this area have several methodologic problems that make it impossible to conclude that prenatal alcohol exposure in animals affects neuroanatomical development. It is interesting that despite differences between studies, a consistent pattern of findings has emerged (i.e., retarded development), which supports Stockard's (1932) explanation of his results nearly 50 years ago. If the results can be confirmed in better controlled studies, it may be safe to conclude that prenatal alcohol exposure temporarily delays development of the brain (and perhaps the entire organism). At this time, it is premature to draw such a conclusion.

### Neurochemical Alterations

Teratogenic effects of alcohol on the brains of animals have been demonstrated at the neurochemical level as well as at the anatomic level. However, as in the neuroanatomical studies, relatively few experiments have been done in this area, and those that have been done are inconclusive and represent the work of only a handful of laboratories. Additionally, all of the studies have used rats or mice and have examined levels of neurotransmitters in whole brain.

The findings with respect to the neurotransmitter serotonin (5-HT) have been the most inconsistent. Rawat (1977) reported no differences in whole brain concentration of 5-HT in 18- or 21-day-old fetuses exposed to alcohol during gestation and pair-fed controls. These findings were confirmed in mice by Boggan, Randall, Wilson-Burroughs, and Parker (1979), who additionally demonstrated no differences between prenatal alcohol and pair-fed pups of various ages on whole brain levels of tryptophan, 5-hydroxyindoleacetic acid concentrations, the rate of 5-HT synthesis, or the rate of 5-HT uptake. On the other hand, Elis and colleagues (1978) and Krsiak and colleagues (1977) reported marked decreases in brain concentrations of 5-HT in the offspring of pregnant mice who received low doses of alcohol during

gestation. The contradictory results from the various laboratories possibly can be explained by different treatment periods, different routes of alcohol administration, different doses of alcohol employed, different ages of test animals, and other methodologic differences.

A similar inconsistency exists in the literature with regard to the catecholamine norepinephrine (NE). Norepinephrine levels have been reported to be elevated (Rawat 1977), decreased (Detering et al. 1978), or unchanged (Elis et al. 1976) in the brains of rat pups exposed to alcohol during gestation. The literature on dopamine is consistent, however. Dopamine concentrations in brains of experimental and control offspring have not been shown to be different (Detering et al. 1978; Elis et al. 1976). Whether the activity of tyrosine hydroxylase, the enzyme that catalyzes the synthesis of norepinephrine from dopamine, is affected is uncertain. Branchey and Friedhoff (1973) reported an increase in activity in the caudate nucleus in experimental offspring, but Thadani and colleagues (1977b) found no change in whole brain levels. It is possible, however, that whole brain assessment masked differences in discrete regions of the brain.

One thing is certain from a review of the literature in this area: no conclusions can be reached. It appears that some alterations have taken place, but more research using similar methodologies and studying neurotransmitter turnover, instead of levels, needs to be done in order to enable a comparison of results from one laboratory to another.

### *Prenatal Alcohol: Effects on Biochemistry*

Sporadic reports have appeared in the literature describing biochemical alterations in offspring exposed to alcohol *in utero*. For example, in the ewe, placental transport of infused alcohol was associated with an initial fetal metabolic acidosis, and later a mixed metabolic-respiratory acidosis that worsened following the infusion period (Mann et al. 1975a). These results imply that maternal alcohol intake is associated with marked changes in not only maternal, but fetal acid-base balance as well. Whether these changes in fetal physiology are responsible for the deleterious effects of alcohol on growth and development remains to be determined.

Since alcohol is metabolized mainly in the liver by alcohol dehydrogenase (ADH) and also by the microsomal ethanol-oxidizing system (MEOS), Sze and colleagues (1976) investigated whether prenatal and postnatal administration of alcohol to C57BL and DBA mice would induce the activity of these enzymes similarly to that seen following chronic alcohol treatment. Their results demonstrated an elevation in both ADH and MEOS levels. Following nearly an identical protocol and using the C57BL/6 mouse strain, Duncan and Woodhouse (1978) were unable to confirm these results. The reason for the discrepancy between studies is unclear. Hopefully, future experiments addressing



the issue of liver enzyme induction in alcohol-exposed offspring will employ nutritional control groups.

Another area of biochemical interest to researchers was the pattern of ornithine decarboxylase (ODC) activity in the heart and brain of fetal and neonatal rats exposed to alcohol beginning on day 11 of gestation (Thadani, Slotkin, and Schanberg 1977). Changes in this enzyme reflect an alteration in polyamine metabolism, which plays a regulating role in protein synthesis. Alterations in ODC developmental patterns were observed in these two tissues indicating that maternal ethanol administration has a marked effect on polyamine metabolism. Such changes may be expected to affect the growth and development of the tissues.

Little is known about the effect of prenatal alcohol exposure on peripheral physiology. One study reported that maternal ethanol ingestion in rats caused a reversible retardation in the maturation of adrenal catecholamine stores (Lau et al. 1976), and a recent study by Rawat (1979) reported an inhibition of cardiac protein synthesis in fetal rat hearts as a function of maternal alcohol treatment. Because of the well-documented effects of ethanol on protein synthesis (Tewari and Noble 1979), this may be a major mechanism by which maternal intake alters fetal growth and development (Henderson et al, 1980; Khawaja et al. 1978; Rawat 1975, 1976).

Obviously, there is a lot to be learned about the biochemical changes that result from prenatal exposure to alcohol. There have been few studies in this area to date, but this is not surprising since initial research efforts were primarily concentrated on proving the teratogenicity of alcohol in animals.

### *Prenatal Alcohol: Miscellaneous Effects*

Among the miscellaneous effects of prenatal alcohol exposure are alterations in fetal body composition and electrolyte content, abnormal fetal cerebral function, and retarded sexual development. More specifically, Abel and Greizerstein (1979) reported that maternal alcohol administration (6 g/kg/day, intragastrically) from day 5 to day 19 of pregnancy was associated with increased fetal body water and sodium content and a decreased lipid-free solid content. A single dose of 6 g/kg on gestation day 20 produced somewhat similar changes in fetal body composition, except that magnesium levels instead of sodium levels were elevated (Greizerstein and Abel 1979).

With regard to the effect of alcohol on fetal cerebral function, Mann and colleagues (1975b) reported that in the ewe the fetal EEG decreased in amplitude as maternal alcohol concentration increased. Fetal cerebral uptake of oxygen was unaffected. Since alcohol is a central nervous system (CNS) depressant, it is not surprising that fetal brain activity is depressed by maternal alcohol administration. It is not clear whether such a depression may result in long-term neurologic deficits that are not reversible. It will be remembered that CNS dysfunction is a major feature of the FAS (Clarren and Smith 1978).

As stated earlier, teratogenic effects need not be demonstrated only at birth. Latent effect may not become apparent until a system or organ becomes functionally mature or until it is challenged. An example of a latent effect of prenatal alcohol is on the sexual development of the female. Farry and Tittmar (1975) and Boggan, Randall, and Dodds (1979) have observed a marked delay in vaginal opening in female mice exposed to alcohol *in utero*. Vaginal opening in the mouse occurs about day 35 (varying somewhat according to strain) and is an excellent biological marker for sexual maturity. Boggan, Randall, and Dodds (1979) reported delays of up to 70 days of age. A delay in sexual development implies a modification in the hormonal system that triggers puberty. This speculation of altered gonadal hormone synchrony remains to be examined, however, as does an evaluation of reproductive function in experimental offspring. While these studies are intriguing and have clinical significance, it should be kept in mind that because fostering procedures were not employed, prenatal alcohol effects cannot be partitioned from postnatal effects.

### ***Critical Discussion and General Conclusions***

Although alcohol has been considered to be a teratogen for nearly 200 years, this review has illustrated how interest in the issue has been cyclic. Studies in the early 20th century were suggestive but did not offer convincing evidence that alcohol was teratogenic. The studies were not designed specifically to address the effect of *in utero* exposure and therefore were plagued with possible confounding variables and were characterized by inadequate control groups. The contribution to the question of whether alcohol is teratogenic or not was minimal at best.

The more recent experiments that have specifically addressed the question are, on the whole, better designed. For example, pair-fed control groups as well as *ad libitum* groups were included in many of the experiments, and some investigators used more than one alcohol dose or strain of animal. On the negative side, only a few experiments used a fostering procedure, which is critical in order to partition prenatal from postnatal effects.

Although many of the experiments were adequately designed, methodologies varied considerably. Consequently, this body of literature is plagued with inconsistent results. Still, some important general conclusions can be drawn.

Alcohol is clearly teratogenic in the classical sense, in that several investigators have demonstrated anomalous morphologic development in animals exposed to alcohol *in utero*. The effect, however, is dose related and is affected by genotype. Low doses of alcohol do not result in any appreciable blood alcohol level and do not produce observable defects of body structure. This is not to say that low doses are not

teratogenic, just that they do not result in grossly observable birth defects.

Body weight is also affected by high alcohol doses. Pups exposed to alcohol prenatally tend to be smaller than control pups at birth. It is less clear whether alterations in the brain and/or biochemical function exist because the experimental findings are either unconfirmed or inconsistent, or the experiments were faultily designed and did not foster the pups at birth. Thus offspring growth and development are clearly adversely affected by maternal alcohol administration, and while it is suggested that CNS alterations and biochemical defects exist, more studies are needed to clarify the issue. The significance of these experiments is that maternal nutritional variables cannot account for the effects observed. Even though these variables cannot be completely ruled out, it can be concluded that alcohol is a teratogen in animals in its own right (Brown et al. 1979).

### ***Future Trends***

Alcohol and animal teratology promises to be a popular field in the next decade for scientists of all disciplines for two reasons. First, current research findings have stimulated ideas and theories that will be investigated for their contribution to an understanding of teratology in general. Second, there will be a focus on animal models to address clinical issues relevant to the fetal alcohol syndrome.

With regard to the latter focus, animal models in future studies will investigate whether critical periods or dosages of alcohol exist, whether alcohol administration to the father can produce defective offspring (Joffe 1979), whether drug combinations during pregnancy are more harmful to the fetus than alcohol alone, whether maternal drinking history prior to conception influences the outcome of pregnancy, and whether the offspring of alcoholic parents respond to alcohol differently than controls (i.e., more or less tolerant). It is likely that rat and mouse models will continue to be used in studies of this type, but the future more than likely will see an emphasis on a primate model as well.

One of the most exciting areas for experimentation in the future is the identification of the mechanism by which alcohol affects fetal development. It has been suggested that acetaldehyde is responsible for the adverse effects observed in both humans and animals (Veghelyi et al. 1978), but this theory needs to be confirmed in better controlled studies that take into account nutritional variables as well as an understanding of alcohol metabolism. While it is well known that alcohol is metabolized to acetaldehyde, it is often forgotten that the reverse reaction takes place. In addition to the role of acetaldehyde, other mechanisms of action that should be investigated include hypoxia, maternal hypothermia, altered amino acid transport across the placenta, and alcohol-related folic acid, zinc, and/or magnesium deficiency. Once the



mechanism of action is identified, it eventually may be possible to intervene therapeutically and prevent alcohol-related abnormal fetal development.

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## Chapter 10





# **Ethanol as a Behavioral Teratogen: Animal Models**

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## **Abstract**

Serious adverse effects of alcohol consumption during pregnancy have been recognized in humans by clinical observations and in animals by controlled laboratory experiments. This paper surveys animal studies investigating the potential of ethanol as a behavioral teratogen, that is, the effect prenatal alcohol exposure might have in altering later behavior in the absence of obvious gross morphological abnormalities. Although animal studies dealing with this question date to the beginning of this century, it is only within the last 5 years that research in this area has increased significantly.

The review of the literature that is presented focuses on alterations in activity, behavioral development, learning and memory, aggression, and behavior towards ethanol as a consequence of prenatal alcohol exposure. While methodological problems are present in many of the studies cited and contradictory evidence is also available, several tentative conclusions are suggested. Prenatal exposure to alcohol appears to cause an increase in general activity which may be age dependent and may delay behavioral and physical development. A substantial number of studies also report effects on learning ability in a variety of tasks. Generally, the alcohol-exposed animals show a deficit relative to controls. Prenatal alcohol exposure has also been reported to increase aggressiveness and preference for alcohol. It is suggested that one consequence of alcohol exposure might be a deficit in response inhibition, although this deficit might diminish as the animal matures.

Following the literature review, methodological considerations for these animal studies are presented. The role of proper nutritional controls, controls for possible alterations in maternal behavior, the question of culling, and appropriate data analyses are among the issues discussed. Finally, directions for future research in assessing the behavioral teratogenic potential of ethanol are suggested.

## ***Introduction***

It has long been suggested that parental alcohol consumption could have deleterious behavioral consequences on offspring. Early in the century, for example, Tredgold (1914) concluded that parental alcoholism was a major cause of mental deficiency in offspring. However, it was open to speculation whether the deficiency was due to alcohol-induced changes in parental reproductive cells, exposure of the embryo or fetus to alcohol, a genetic abnormality causing both alcoholism and a predisposition to have mentally deficient children, or environmental factors. To decide which of these possibilities was responsible, researchers turned to animal studies.

Arlitt (1919) concluded from experiments with rats that chronic administration of medium or large doses of alcohol to both parents resulted in progeny deficient in maze learning. MacDowell (1923) reported that rats born to parents treated with alcohol had fewer perfect trials in a complex maze than rats born to parents not treated with alcohol. Treatment of the father alone did not cause behavioral alteration in the offspring, implicating maternal alcoholism as a crucial factor. However, findings of deficient performance were not universal. As pointed out by Hanson and Cooper (1930), MacDowell himself in an earlier study had found enhanced performance in offspring of alcohol-treated parents.

Several other reports are interesting from a historical point of view. Mirone (1958) found an enhanced preference for alcohol in mice whose parents had consumed an alcohol solution. In the same year, Vincent reported that pregnant rats intubated with alcohol (i.e., administered alcohol by stomach tube), gave birth to offspring with inferior learning ability. He also noted that exposure to a low dose of alcohol resulted in a decrease in "emotionality," while exposure to larger doses increased this trait. However, these observations must be viewed cautiously. As Morra (1969) has suggested, the results of Vincent's experiments may have been due to an interaction of alcohol with the stress of intubation.

These and other early investigations often had methodological problems. Controls for possible alcohol-induced alterations in maternal behavior were not included. Nutritional controls were frequently lacking and alcohol often was not administered in uniform doses. Furthermore, alcohol was often administered to both parents, thus confounding any effects of paternal alcohol exposure with the effects resulting from exposure in the uterus. Perhaps for these reasons, studies of this nature did not attract a great deal of attention or stimulate much additional research.

It was not until after 1973 that research interest in the effects of prenatal alcohol exposure was increased by two reports of a common pattern of abnormal growth in the offspring of chronically alcoholic women (Jones and Smith 1973; Jones et al. 1973). This distinctive pattern of abnormalities, which has been named the fetal alcohol



syndrome (FAS), includes some central nervous system dysfunction, such as microcephaly or mental retardation, prenatal and postnatal growth deficiencies, and distinctive facial characteristics including small eye openings.

Other studies published since these initial reports make it clear that the effects of prenatal alcohol exposure lie on a continuum. On one end of the continuum are the very noticeable effects, such as death of the infant near the time of birth or the gross morphological anomalies associated with FAS; on the other end are perhaps only subtle behavioral changes (Clarren and Smith 1978; Shaywitz 1978). This review is concerned with the latter, that is, with alcohol as a behavioral teratogen. A behavioral teratogen can be defined as any agent capable of causing alterations in normal behavior without causing gross morphological defects when administered during prenatal development.

Animals are frequently used in studies of behavioral teratology because they allow a degree of control that is not possible in either retrospective or prospective investigations in humans. Many of the complexities inherent in human studies can be minimized by an appropriate animal model. Experimenters working with animals can control for genetic variables and need not worry about the confounding effects of other drug use, both of which are problems in human research. Time of administration, dosage of alcohol, postnatal environment, and maternal nutrition (an extremely important factor) can also be controlled. Finally, for a variety of reasons, animal studies allow a greater range of tests than would be possible with humans.

This paper begins with a review of the literature. In hope of clarifying the many inconsistencies in the literature, the review is followed by an analysis of the procedural inadequacies of many of the studies. Finally, attention is directed to considerations that behavioral scientists interested in alcohol may wish to address in the future. Since many of the studies discussed investigated a variety of behaviors, they are cited in several sections. However, the pertinent procedures are described only the first time the studies are mentioned. Several studies where alcohol was administered both prenatally and postnatally are not cited, since the influence of early postnatal alcohol exposure on behavior is beyond the scope of this review.

## ***Alcohol and Behavioral Teratology: A Review of the Literature***

### ***Effects on General Activity and Reactivity***

Behavioral scientists have long relied on activity measurements to assess animal behavior. One of the most common methods of measuring activity is the open field, which is simply a large enclosed arena marked off in equal segments. The animal is placed in the arena and the number of segments it enters within a specified period of time is

recorded. Often, rearing behavior (how frequently the animal rears on its hind legs) and defecation are also measured.

One of the first reports after FAS was identified in 1973 was an investigation of behavioral changes in rats whose mothers were fed a liquid diet containing alcohol from the 10th day of gestation through parturition (Branchey and Friedhoff 1976). In comparison to a control group whose mothers received the same diet without alcohol, the alcohol-exposed progeny were significantly more active in the open field. However, this study did not control for the possible effects of the liquid diet (e.g., reduced intake of calories), nor did it control for possible alterations in postnatal maternal behavior.

Bond and DiGiusto (1976) also used the liquid diet technique to administer alcohol to pregnant rats. The offspring were tested in an open field on 3 successive days. In contrast to rats whose mothers had access to standard lab chow, the alcohol-exposed rats were more active and reared more frequently. Furthermore, the alcohol-exposed progeny increased their activity over the 3-day test period, while the activity of the control group remained relatively constant. In a followup study, Bond and DiGiusto (1977a) concluded that the increase in activity was age-dependent. The procedures were similar to those used in their previous study except that offspring were tested at three different ages for 10 consecutive days. Heightened activity relative to control animals was found in alcohol-exposed progeny when they were young, but not when they became adults. Controls for nutritional effects or for any effects of alterations in postnatal maternal behavior were not included in either study.

Several investigators have used intubation rather than a liquid diet to administer alcohol to pregnant rats. For example, Abel and York (1979), in an extremely well-controlled study, intubated either 1 or 2 grams of ethanol per kilogram of body weight (g/kg) to rats throughout their pregnancies. No significant differences were found in general activity or in rearing in a single 3-minute trial in the open field at 75 days of age. In a similar study, Abel (1979a) increased the alcohol dose levels to 4 and 6 g/kg and again found no significant differences in general activity between groups, although offspring of females that received the 6-gram dose reared less than their pair-fed controls.

On the other hand, Caul et al. (1979) found increased open-field activity in the offspring of pregnant rats intubated with 6, 4, or 2 g/kg ethanol twice daily in equally divided doses. Pair-fed and lab chow control groups were included in the design. At 63 and 64 days of age, open-field behavior was recorded for 5 minutes. On the second test day, the 4 g/kg group showed more activity than the control groups, although it is obvious from the data that differences also existed between the pair-fed and nontreated control progeny. Rearing behavior showed similar trends. In a second experiment with no control groups, an 8 g/kg group was added. No differences in ambulation were seen when the animals were placed in the field, although offspring of the 8



g/kg group moved sooner and reared and groomed more than the other alcohol-exposed progeny.

In a subsequent investigation (Osborne et al. 1980), this research group attempted to remedy some of the methodological problems of their previous study by controlling for postnatal mothering behavior in the alcohol-fed rats. This was accomplished by cross-fostering, a procedure in which some offspring from alcohol-exposed mothers are reared by control mothers and some unexposed offspring are reared by mothers who had received alcohol during pregnancy to determine if the alcohol exposure had altered maternal behavior. Mothers were intubated with 4 g/kg twice a day. When open-field activity was assessed, the alcohol-exposed offspring had increased activity relative to controls. Since cross-fostering procedures were used, the increased activity appeared to arise from prenatal alcohol exposure, not from postnatal rearing condition.

Another apparatus frequently used by behavioral scientists to measure activity is the running wheel. Activity is measured by counting the number of times the animal rotates the wheel. In a well-controlled study using this apparatus, Martin et al. (1978) found heightened activity in male rats whose mothers were intubated daily with 8.5 g/kg of ethanol in two divided doses throughout gestation. At 2 months of age the offspring were tested for running-wheel activity during a 16-hour period.

A variety of activity measurements have been used by several other investigators. For example, Riley, Shapiro, and Lochry (1979) investigated nose-poking and head-dipping behaviors in rats prenatally exposed to alcohol. These activities are presumed to be exploratory and to be independent of general arousal and ambulatory tendencies. During gestation, rats were fed liquid diets containing various amounts of ethanol. A control group was fed a nonalcoholic liquid diet that was isocaloric (i.e., contained the same amount of calories), and a pair-feeding procedure was included to ensure equal intake of calories between the groups. Another group of females was maintained on standard lab chow as a further control.

At 29 days of age, male offspring were tested for their tendency to poke their noses into a small cylinder projecting from one wall of a small dark cubicle. During the test period, alcohol-exposed progeny poked sooner and more frequently than those whose mothers were given no alcohol. Furthermore, the frequency of nose-poking was related to the extent of prenatal exposure to alcohol: the greater the prenatal exposure, the more nose-poking. A second study showed that heightened nose-poking of alcohol-exposed progeny was not altered by extensive postnatal handling.

In a third experiment it was found that prenatal alcohol exposure also increased head-dipping in a dose-related manner. Head-dipping is similar to nose-poking except that the animal dips its head into holes in the floor of the apparatus. Altered postnatal maternal behavior cannot



be ruled out as a contributing factor to these effects, however, since all litters were raised by their biological mothers.

Shaywitz and colleagues (1976) used a video system to record the percentage of time animals were active. Pregnant rats were fed either a liquid diet containing alcohol or an isocaloric nonalcoholic diet. Animals born to mothers receiving alcohol were more active at 12 and 19 days of age, but not at 26 days of age. A followup study with similar procedures (Shaywitz et al. 1979) found no statistically significant changes in activity in successive measurements at 12, 15, 19, or 23 days of age in the prenatally exposed animals, although their mean activity scores at the latter three ages were always higher than those of control animals.

Acoustic startle behavior was used by Anandam et al. (1979) to measure activity in rats prenatally exposed to alcohol. The outcome of this study supports the notion that prenatal alcohol exposure results in hyperreactivity. Pregnant rats were intubated twice daily with a 4 g/kg dose of ethanol and their offspring were compared with those of a pair-fed group and a group allowed free access to standard lab chow. Offspring were raised by their own mothers, but observations of maternal behavior indicated no difference in pup retrieval during the first week after birth. At 30 days of age, female offspring were tested for differences in startle response to a loud, shrill tone (110 dB, 8 kHz). The ethanol-exposed progeny showed more vigorous startle reactions to the tone.

Three studies already discussed also included miscellaneous activity measures. Osborne et al. (1980) reported that during testing of Y-maze discriminated avoidance, where an animal must choose between two goals to avoid an electric shock, offspring prenatally exposed to alcohol were more active between trials than either pair-fed or nontreated controls. Again, cross-fostering did not significantly alter the results. On the other hand, Abel and York (1979), who reported no differences in open-field activity in offspring receiving 1 or 2 g/kg of ethanol during pregnancy, also found no differences in free-field activity (a modification of the open-field measure). Furthermore, in the study using 4 and 6 g/kg doses, Abel (1979a) found that male offspring of the 6 g/kg group took longer to step down from a 7.5 cm-high platform (step-down latency) than pair-fed controls did, a finding contrary to the notion that prenatal exposure to alcohol increases activity in offspring. (Differences in step-down latency in females were not significant.)

Many of the studies described above have some methodological problems, such as a lack of any control group, a failure to account for differences in nutritional status between groups, and a failure to control for possible alcohol-induced alterations in maternal behavior. (These problems are discussed in more detail in a later section.) Despite these shortcomings, the findings of these studies, taken collectively, lead one to suspect that prenatal exposure to alcohol increases activity and/or exploratory tendencies as well as reactivity.

Furthermore, there is some indication that these effects are age-dependent and diminish as the animal matures, a finding that may help to reconcile some of the contradictory results. Another point that could help reconcile contradictions is that in at least two of the above studies the differences in activity between alcohol-exposed and control progeny increased with repeated testing. In studies where differences in activity were found, testing consisted of multiple sessions or a single long session. In contrast, only a single short session was employed in studies where differences were not found, and it is possible that differences would have been revealed by repeated testing.

Finally, while it seems that prenatal alcohol insult causes an increase in activity, it is still unclear exactly what underlying processes are being assessed. For example, activity measured in the open-field test often does not correlate with running-wheel activity, obviously indicating that the two apparatus may not measure the same underlying process. Likewise, open-field scores have been used to reflect "emotionality," "curiosity," or "habituation," indicating disagreement over what increased activity in the open-field procedure actually reflects or its relation to other activity measures.

### *Effects on Behavioral, Motor, and Sensory Development*

In their 1976 report, Shaywitz et al. reported that the offspring of mothers that consumed alcohol during their pregnancies showed some delay in the maturation of the righting reflex and in the age of eye-opening. However, the same investigators reported later that they were unable to replicate their previous findings (Shaywitz et al. 1979).

Demers and Kirouac (1978) found that rats exposed prenatally to alcohol were delayed on 6 of 13 indexes of developmental maturation. Unfortunately, it is difficult to generalize from this study, because very few litters were used and nutritional controls were lacking.

Several developmental indexes were also assessed in the running-wheel study by Martin et al. (1978). Prenatal exposure to alcohol did not significantly affect the righting reflex, the distance traveled forward in 5 seconds, or the time of first appearance of incisor teeth. However, in comparison to controls, fewer alcohol-exposed progeny showed unfurling of ear flaps on the 3rd day of life. Similarly, fewer had their eyes open on the 14th day, although cross-fostering to surrogate mothers increased the number of offspring who had their eyes opened at that time in both alcohol-treated and control groups.

Recently, Lee et al. (1980) reported several developmental delays in rats whose mothers were administered alcohol in a liquid diet during pregnancy. Compared to controls, the rats were delayed a day or more on surface righting, negative geotaxis, and eye-opening. Postnatal maternal factors were controlled for in this study by rearing all animals with nontreated surrogate mothers.

On the other hand, several investigators have reported that alcohol did not affect developmental parameters. Caul et al. (1979) found that

alcohol had no effect on the presence of hair or teeth, eye-opening, quality of walking, and grooming behavior. Tittmar (1977) reported no effects on ear-unfurling, incisor eruption, or eye-opening. Anandam et al. (1979) also found no effect on several developmental measures.

Motor coordination was examined in a well-controlled study by Abel and Dintcheff (1978). The mothers were intubated with 4 g/kg or 6 g/kg of alcohol throughout pregnancy, and some of the offspring were tested at 16 days of age for their ability to stay on an inclined plane. Offspring whose mothers received the 6 g/kg dose fell off the incline at a less steep angle than either the pair-fed or untreated control animals. The 4 g/kg dose had no significant effect. Some of the animals were also tested on a Rotarod, an accelerating rotating drum, at 20 days of age. In this case both alcohol groups stayed on the drum for less time than either the pair-fed or untreated control groups. (The pair-fed and untreated control animals performed equally in both the inclined plane and Rotarod tests.)

When rats are placed in a T-maze, they generally alternate their entry into each arm of the "T" on successive trials. This tendency generally develops between 18 and 22 days of age. Riley, Lochry, Shapiro, and Baldwin (1979) found that the pattern was disturbed in 21-day-old rats prenatally exposed to alcohol. In comparison to controls, the alcohol-exposed rats took more trials to enter the arm opposite the one they had previously entered. Furthermore, the number of trials was proportional to the concentration of alcohol in the mother's liquid diet. One interpretation suggested by the authors is that alcohol delayed maturation, causing the alcohol-exposed rats to behave as a less mature rat would. Interestingly, Abel (1978, 1979a) reported that this deficit in spontaneous alternation did not occur when animals were tested as adults, a finding that is consistent with the hypothesis that prenatal alcohol exposure delays behavioral maturation. However, several procedural differences between the studies make alternate explanations equally plausible.

Obviously, much of the data concerning various developmental characteristics are contradictory. Furthermore, it is difficult to come to any firm conclusions since nutritional controls often were inadequate and postnatal maternal behavior was not always controlled. Nevertheless, some tentative suggestions can be made. Early exposure to alcohol may delay development, especially the development of behavioral tasks such as spontaneous alternation in a T-maze and motor coordination. Delays in simple age-related developmental characteristics, such as age of righting reflex or of incisor eruption, appear to be less prevalent.

### *Effects on Learning and Memory*

In view of the intellectual deficits reported in children with FAS, it was natural for behavioral scientists to study potential cognitive deficits in various animal models. One such study was done by Arroux and



Dehaupas (1970, as cited in Abel 1980). Testing by means of a shock-avoidance task at about 45 days of age, they reported that rats whose mothers had consumed a 15 percent ethanol solution throughout gestation performed significantly better than offspring whose mothers drank only water. However, the more usual finding in this type of study is that prenatal alcohol exposure results in a deficit in avoidance learning.

Shaywitz et al. (1976) reported impaired shuttle-box performance in offspring prenatally exposed to alcohol, but it is unclear whether a one-way or two-way avoidance procedure was used. In the one-way task, one side of the apparatus is always the safe side, and the animals must learn to run to it from the side where shock is administered and do it within a specified time to avoid shock. In the two-way task, shock can be delivered to either compartment, and to avoid shock the animals must learn to shuttle from whatever side they are in to the opposite side within a specified time.

Using the liquid diet technique, Bond and DiGiusto (1977*b*) reported a deficit in two-way avoidance as a consequence of prenatal exposure to alcohol in rats. The alcohol-exposed offspring avoided the shock on 30 percent of the trials compared to 45 percent for offspring whose mothers were fed lab chow. The two groups did not appear to differ in activity level or pain sensitivity. Since the animals were raised by their biological mothers, the authors later extended their study by including fostering and cross-fostering techniques to rule out the possibility that these differences were due to alcohol-induced differences in maternal behavior (Bond and DiGiusto 1978). Again, the alcohol-exposed animals were found inferior in shock avoidance.

Two-way avoidance was also examined by Abel (1979*b*) using 4 g/kg and 6 g/kg daily doses by intubation to pregnant rats. The alcohol-exposed female offspring appeared to be significantly impaired in a dose-dependent manner. No differences were found in the males, but this may be due to the inadvertent use of a smaller sample size. Thus Abel's study partly supports the previous work of Bond and DiGiusto and included adequate nutritional controls and surrogate fostering procedures.

In another study, Abel (1978) measured one-way avoidance in rats prenatally exposed to alcohol. The rats, whose mothers were intubated with 1 and 2 g/kg doses of alcohol throughout pregnancy, showed no impairment of one-way avoidance. Shaywitz et al. (1979) also examined one-way avoidance and found evidence that seems to indicate poorer performance in prenatally exposed rats. However, statistical support for this finding was not presented.

Another technique used in behavioral studies is the measurement of passive avoidance. In contrast to one-way and two-way avoidance, passive avoidance requires the animal to inhibit a response in order to avoid some unpleasantness. Riley, Lochry, and Shapiro (1979) examined passive avoidance behavior in two experiments with rats whose mothers had consumed liquid diets containing various amounts of alcohol. In the first study, 18-day-old female offspring were placed in the

bright side of a two-compartment chamber. If the animal crossed into the other compartment before 180 seconds elapsed, a mild shock was administered. The number of trials it took for prenatally exposed rats to learn this increased according to the amount of alcohol fed to their mothers. The effect was pronounced in these younger animals, but when older rats (approximately 45 days of age) were tested they tended to approach the performance level of unexposed controls.

In the second experiment, 21-day-old female offspring were placed on a restricted fluid regimen and were then allowed access to a lithium chloride solution. Under these circumstances, rats normally form a strong aversion to the noxious solution and consume very little of it on its second presentation. This situation is a passive avoidance model because an animal must withhold a drinking response to avoid illness. It was found that alcohol-exposed offspring drank more of the lithium chloride solution on its second presentation than the controls did. All animals were raised by their biological mothers, however, so the differences could have been due to altered maternal behavior.

Recently, Lochry and Riley (1980) replicated the shock-motivated passive avoidance data of their earlier study (Riley, Lochry, and Shapiro 1979) and again found that the degree of deficit in alcohol-exposed offspring depended on the amount of alcohol the animals' mothers received during pregnancy. This study also showed that although alcohol-exposed rats took longer to acquire the passive avoidance response, once they acquired it they retained it as well as control animals. No differences between any groups were noted during retention tests conducted 1, 3, or 7 days after the passive avoidance response was acquired.

Other methods frequently used by behavioral scientists to measure alcohol impairment are discrimination-learning and maze-learning. In their 1976 report, Shaywitz et al. found impaired T-maze learning in 21-day-old rats born to mothers who consumed alcohol during their pregnancies. In their followup study (1979), they also noted impaired escape behavior in such rats when tested at 22 days of age. No data for the number of correct choices were provided, however, so it is not known if differences in motivation might account for these results.

Abel (1978) could find no difference in brightness discrimination between prenatally exposed rats and control rats. In this study the mothers were intubated with either 1 or 2 g/kg doses of ethanol throughout gestation, and pair-fed control mothers and surrogate mothers were included in the design. When tested as adults, the offspring could escape a mild shock by running to the illuminated arm of a T-maze. Entries to the darkened arm were considered errors. All of the groups learned the task at the same rate.

Riley, Lochry, Shapiro, and Baldwin (1979), using a spatial discriminated-escape test, also found no difference in performance in female offspring whose mothers received liquid diets containing various amounts of alcohol during pregnancy. However, when the animals were reversed and required to run to the opposite goal, the alcohol-exposed



progeny made more total mistakes and more mistakes per trial than the control offspring. The number of mistakes was related to the amount of alcohol the mothers received during pregnancy.

More recently, Lochry and Riley (1980) did find differences during acquisition of the same task using a different acquisition criterion. During acquisition the alcohol-exposed progeny made more mistakes than the control progeny. When tested for retention 24 hours later, alcohol-exposed offspring again made more mistakes than the control offspring when the retention test was reversal learning. Furthermore, when retention testing consisted simply of measuring reacquisition of the original response, the alcohol-exposed progeny still made significantly more mistakes than the control offspring, although the magnitude of this deficit was not large.

Acquisition and reversal of a T-maze acquisition task were also investigated by Anandam et al. (1980). Pregnant rats were fed a liquid diet containing ethanol. Control females were either pair-fed an isocaloric nonalcoholic liquid diet or were maintained on standard lab chow. T-maze training consisted of the acquisition, reversal, and retention of a left-right discrimination. In the T-maze, alcohol-exposed progeny were deficient in both the acquisition and reversal phases when compared with either control group.

In contrast to these findings of no effect, or of a deficit in discrimination, the group at Vanderbilt University has reported enhanced discriminated-avoidance learning in prenatally exposed offspring (Osborne et al. 1980). As previously mentioned, these investigators used the intubation procedure and employed cross-fostering and fostering controls. Y-maze avoidance training was started at 65 days of age. In this task animals had to learn to run into the bright arm of a symmetrical Y-maze within 10 seconds after a light was turned on in order to avoid shock. If an animal failed to avoid the shock, it could subsequently escape it by running into the bright arm. This apparatus is unique in that both discriminated-avoidance and escape can be assessed simultaneously, and associative and nonassociative factors responsible for differences can be identified. Ethanol-exposed offspring made more avoidance responses and correct discriminations than either pair-fed or ad lib controls. Postnatal maternal condition did not exert a significant effect.

A more difficult discrimination-learning task was assessed by Abel (1978, 1979b) in a six-unit water-T-maze. If these two studies are taken together, doses of ethanol used were 1, 2, 4, and 6 g/kg. In no case were there significant differences between alcohol-exposed and pair-fed control progeny in the number of trials to a perfect run, or in the number of errorless trials. However, over the 2 days of training, the 2 g/kg group appeared to have a greater degree of transfer from the first to the second day of training than did its pair-fed control group or the ad lib control group. Bond and DiGiusto (1978) also examined maze learning in their study. They found no differences between alcohol-



exposed and lab chow control subjects in ability to learn a Hebb-Williams maze.

Recently, Riley, Shapiro, Lochry, and Broida (1980) have used an operant-learning task to assess the behavioral teratogenicity of alcohol. Pregnant rats were given liquid diets containing various concentrations of ethanol (35, 23, 11, or 0 percent ethanol-derived calories). Food-deprived male offspring were taught to press a bar to obtain a small pellet of food. After the animals acquired this response, the number of times they had to press the bar to receive food was increased every fourth day, until finally they had to press the bar 33 times to get this reinforcement. (This requirement is referred to as FR-33, and this study is referred to below as the FR study.) After 3 days at FR-33, the rats were given six extinction sessions during which pressing the bar no longer produced food. During acquisition of the response, the offspring of rats that received 35 percent ethanol during pregnancy consistently had the lowest response rates, while the 0 percent alcohol group had the highest. The intermediate alcohol groups had response rates between these two groups. However, when extinction began and responses no longer produced reward, this relationship was reversed. Now, the 35 percent group had the highest response rates, and the 0 percent group had the lowest. Again the intermediate alcohol groups had intermediate response rates.

Riley, Driscoll, and Chen (1980) have examined DRL performance (differential reinforcement of low rates of responding) as a consequence of prenatal alcohol exposure. With a DRL schedule, an animal must learn to inhibit a bar-pressing response for a specified time (10 seconds in this study) before pressure on the bar brings food. Thus, to maximize the rate of food delivery, the animal should press once every 10 seconds (DRL-10). It was hypothesized that alcohol-exposed animals might have difficulty in withholding responding and therefore perform poorly. The opposite occurred: Initially, the alcohol-exposed animals had lower response rates than the control animals and therefore received more food. These lower response rates as a result of prenatal alcohol insult are similar to those noted in the FR-study by Riley, Shapiro, Lochry, and Broida (1980). However, after about 30 days of training, the control animals began to outperform the alcohol-exposed offspring as their timing behavior improved at a faster rate.

In summary, a large number of studies have found impaired learning ability in animals exposed to alcohol prenatally. The most consistent findings, those that have been replicated, are deficits in two-way and passive avoidance and in the acquisition and reversal of simple discriminations. More tentative findings include lowered operant response rates and increased resistance to extinction.

It should be stressed that (1) several studies have failed to find differences and (2) the reasons for these discrepancies are not clear. It should be obvious, though, that differences in test procedures, modes and doses of alcohol administration, and age of testing will influence the outcome of any study. Furthermore, any disparity between treated and

untreated offspring in performance of tasks does not necessarily imply cognitive deficits resulting from prenatal alcohol exposure, because differences in activity or motivation also may account for these findings.

### *Effects on Aggression*

In 1975, Elis and Krviak reported that the mice of mothers intubated with a 1 g/kg dose of ethanol throughout their pregnancies were significantly more aggressive to other mice. No differences between groups were found for measures of social activities (e.g., sniffing, climbing), timid behaviors (e.g., escapes), or individual behaviors (e.g., self-grooming). Pair-feeding was not used, and the young mice were raised by their biological mothers. In a later study, Krviak et al. (1977) studied aggressive behavior in rats and again noted increased aggressiveness in prenatally exposed progeny. The magnitude of the aggressiveness increased with repeated interaction with other rats. Again, no differences were found in sociable and timid behaviors.

### *Effects on Later Alcohol Preference and Alcohol Sensitivity*

In their study of the influence of prenatal alcohol exposure on open-field behavior, Bond and DiGiusto (1976) also examined alcohol preference in the progeny and found that animals so exposed had greater preference for low concentrations of ethanol than control animals whose mothers were maintained on lab chow. On the other hand, Abel and York (1979) found no effects on subsequent alcohol preference when the offspring were tested at about 150 days of age. One possibility for this discrepancy is that the doses of alcohol administered to the mothers in this latter study were small (1 or 2 g/kg). It should also be noted, however, that this study was the only one that included nutritional and fostering control.

Two studies examined the influence of early alcohol exposure on later sensitivity to the drug. Anandam et al. (1980) reported that while alcohol-exposed offspring did not differ in sleep time after a hypnotic dose of alcohol, they were less hypothermic than control offspring (i.e., their body temperatures did not go down as much). Boggan and Randall (1980) also found no effect on sleep time in alcohol-exposed progeny. At this time it appears that sleep time following an alcohol challenge is not affected by prenatal alcohol exposure. However, the effects on hypothermia are intriguing and need to be replicated.

### *Conclusions*

While there is not always agreement in the literature, it does seem that prenatal alcohol exposure can affect later behavior. Activity levels, developmental parameters, and performance on various learning tasks can be altered by prenatal alcohol exposure. What appears to be missing, though, is a theoretical framework that explains the various findings.

In an attempt to explain their results, Shaywitz et al. (1976) suggested that maternal alcohol ingestion may produce in the offspring hyperactivity that diminishes with age as well as cognitive deficits that persist. More recently Riley and his associates have expanded on this premise (Riley 1980; Riley, Driscoll, and Chen 1980; Riley, Lochry, and Shapiro 1979; Riley, Lochry, Shapiro, and Baldwin 1979; Riley, Shapiro, and Lochry 1979). They suggest that one consequence of prenatal alcohol exposure is a deficit in the ability to withhold responding. This hypothesis not only accounts for much of the data collected by these investigators but also for some of the behavioral data collected by others. For example, if animals lacked inhibitory tendencies, one would expect increases in general activity. Furthermore, one would expect the disparity between alcohol-exposed and control progeny to increase over time as other inhibitory influences, such as fear, diminish. Such an outcome has been reported by Bond and DiGiusto (1976).

A model of this kind would also predict poor performance during reversal learning since this task requires the animal to inhibit responding to a previously correct stimulus. Anandam et al. (1980), Riley, Lochry, Shapiro, and Baldwin (1979), and Lochry and Riley (1980) have reported deficits in reversal learning. Increased resistance to extinction (Riley, Shapiro, Lochry, and Broida 1980), as well as the enhanced discriminated avoidance reported by Osborne et al. (1980), are amenable to this interpretation, as are increases in aggression (Krviak et al. 1977).

Even the finding that prenatally exposed animals consume more alcohol than control animals when given a choice can be explained by this hypothesis. Since alcohol taken orally can act as a "poisoning" agent, an aversion to an alcohol solution might occur in control animals, whereas treated animals would be unable to inhibit responding and would therefore consume more alcohol.

If one considers that this deficit in inhibitory tendencies may result from a developmental delay that retards both physical and behavioral maturation—and diminishing as the animal matures—even more data can be accounted for. With this assumption, the age-related changes in activity, passive avoidance, and spontaneous alternation could be explained. Furthermore, it would explain why alterations in behavior were often found when alcohol-exposed progeny were tested early in life but less frequently in progeny that were tested as adults.

While this interpretation does reconcile some of the discrepancies in the literature, a temporary deficit in response inhibition is obviously not the only effect of prenatal alcohol exposure. For example, the hypothesis does not predict differences during discrimination learning, and, contrary to the empirical findings, it predicts enhanced two-way shuttle avoidance. Other consequences of prenatal alcohol exposure, such as cognitive deficits or alterations in motivation, must be proposed to fully account for the available data.



## ***Methodological Considerations***

Uncontrolled factors that might have influenced the results were present in many of the studies reviewed in the preceding section. Perhaps the most critical factor that has to be considered in behavioral teratology studies on alcohol is the altered nutritional status of the pregnant animal and the fetus. Since alcohol can decrease food and water intake and affect the absorption of nutrients, it is imperative to determine if any of the behavioral effects are the result of malnutrition.

The most common way to deal with this problem is to use two levels of control. One control group should be pair-fed; that is, they should receive the same number of calories per day as the alcohol group by substituting calories from a substance such as sucrose for alcohol calories. The second level of control should be a group allowed to feed at will on standard lab chow, to allow any effects of the liquid diet itself (e.g., reduced caloric intake) to be determined. With these two levels of control, alcohol exposure can be assumed to have an effect if the alcohol-exposed offspring differ from both control groups and if the two control groups do not differ from each other.

Frequently, one of these control groups was not included in the studies outlined (Bond and DiGiusto 1978; Shaywitz et al. 1979). It should be pointed out, however, that while these two levels of control are necessary for any study, they are not sufficient for ruling out nutritional factors. Since alcohol affects the absorption and utilization of nutrients, the alcohol group may still be malnourished when compared with a pair-fed group. This can be critical if the pregnant animals are being fed a diet that is only marginally meeting their needs.

Another factor that has to be considered in behavioral teratology studies is the consequence of being raised by a mother who has been treated with alcohol during her pregnancy. If the mother's behavior or her capability of caring for the young are altered by the alcohol treatment, this could affect the development or even the viability of the offspring. For example, Abel (1978) reported that mothers that had received 2 g/kg of ethanol throughout their pregnancies took longer to retrieve their young than either pair-fed or lab chow control mothers. Testing was conducted during the first day of life approximately 24 hours after the last alcohol dose. Abel (1979c) also found a higher incidence of neonatal cannibalism in mothers treated with alcohol during their pregnancies. Both alcohol- and pair-fed mothers cannibalized their offspring on the first day after birth, but only the alcohol-fed mothers showed cannibalism on the second day as well.

To circumvent these problems, fostering procedures should be included in the experimental design. Ideally, either all the offspring should be fostered to untreated surrogate mothers or cross-fostering should be done on half of the litters. Frequently, controls of this type have not been included (Riley, Driscoll, and Chen 1980; Riley, Lochry, and Shapiro 1979; Riley, Lochry, Shapiro, and Baldwin 1979). However,

in all fairness, when fostering controls have been included in behavioral studies with the aim of examining possible alterations in maternal behavior, frequently no effect has been noted in the behavior of offspring (Martin et al. 1978; Osborne et al. 1980).

Another variable often overlooked by behavioral teratologists working with alcohol is the physical condition of the offspring. Animals prenatally exposed to alcohol are often underweight, and their smaller size may influence any behavioral differences found between them and control animals. For example, smaller animals have been shown to have lower shock thresholds than larger animals (Pare 1969). Thus alcohol-exposed and control groups might not be equivalent in terms of motivational level on tasks that use aversive stimuli. Similarly, as pointed out by Abel (in press), if the groups are deprived of food, they may not be equally motivated.

One area that was not addressed in the literature review is appropriate statistical analysis of data. A frequently encountered error is treating all of the offspring as individual subjects in the analysis. In experiments with animals that give birth to multiple offspring, it is necessary to consider the correlation that can occur between littermates on any particular trait, because littermates theoretically share 50 percent of their genetic makeup as well as the same intrauterine and postnatal environment. Erroneous conclusions could be reached if one large or aberrant litter affected the results.

Several methods can be used to control for this potential statistical artifact. The first would be to analyze the effect of variation between litters and compensate for this variation in the experimental design. Thus one would determine if variation between litters is significant, then use appropriate statistical procedures to correct for it. An alternative approach would be to test each animal in a litter and use the mean of all individual scores for each sex as a statistical unit. A third approach would be to simply test one subject of each sex from each litter.

It should be obvious by now that these procedures all require a large number of litters in the experimental design. One cannot treat 2 rat mothers with alcohol, run 2 controls, test all 20 or 30 offspring, and assume that the sample size for each group was the same as the number of offspring. Rather, unless the litter effect proved insignificant the sample size would be two. Abbey and Howard (1973) and Denenberg (1977) have discussed this problem in detail.

Deciding how many offspring from each litter should be tested brings up the problem of culling. Since litter size may affect body weight and the behavior of mothers and their offspring, the number of young in each litter should be standardized by culling. However, the question of how this should be done remains unanswered. Young animals can be discarded either randomly or culled on the basis of a criterion such as body weight or appearance. In teratology research it is recognized that not all specimens within a litter will be equally affected by a particular treatment. This no doubt applies when one is looking for behavioral teratogenic effects. If animals are randomly culled, it is possible that the

most affected offspring will be discarded. It has been argued by Abel (in press) that in fetal alcohol work one should perhaps retain offspring with characteristics of FAS such as low birthweight. However, one does this at the risk of having any observed behavioral change be the result simply of an animal's small physical stature.

Another question that is occasionally raised concerns the most appropriate method for administering alcohol to the pregnant animal. Three methods are in common use: intubation, liquid diets, and alcohol in water as the only source of fluid. Intubation has the advantage of giving specified amounts of alcohol to the animal, since the animal cannot regulate its intake or its pattern of intake. One disadvantage of this procedure is the stress it causes in the animals. Another disadvantage is that the high initial rise in blood alcohol concentration produced by intubation is not maintained, and for a large part of each day the levels may be extremely low or absent. This problem is especially serious when one considers that many steps in fetal development occur very rapidly and may be underway at a time when blood alcohol levels are not high enough to exert an effect. To circumvent this problem some investigators administer the alcohol twice a day.

The liquid diet method does not involve the direct physical stress that accompanies intubation and has the further advantage of allowing the animal continuous access to alcohol. By adjusting the caloric density of the diet, blood alcohol levels can be maintained throughout the day (although they may reach peak levels at night). Another advantage is that with appropriate composition a nutritionally adequate liquid diet can be administered along with the alcohol. The disadvantage of this method is that the dose of alcohol in grams per kilogram of body weight is unspecified. Since the diets are composed to make alcohol provide a fixed percentage of their total caloric content, the amount of alcohol administered depends on how much of the liquid is consumed. Difficulty may then arise from differences in total daily alcohol consumption and pattern of daily intake among animals in the same group, as well as from day-to-day variations in the intake patterns of individual animals. Another disadvantage, pointed out by Abel (in press), is that the animals are forced to consume a large amount of fluid to maintain sufficient caloric intake.

One problem this author has noted in experiments using liquid diets is a difference in daily intake patterns between animals on the diet containing alcohol and their pair-fed controls on the nonalcoholic diet. The animals receiving diets containing alcohol tend to consume them throughout the day, although they do consume more at night. The pair-fed controls, however, tend to consume a fair amount of the diet when it is first presented and consume the rest at night. What effect this difference in intake pattern may have is not known. Nor is it known whether this problem is unique to the liquid diet method or may occur in any pair-feeding situation. For example, when intubation is used, the alcohol-treated mothers have free access to standard chow while the



pair-fed animals have limited access. Thus, differences in consumption patterns could occur.

The other procedure that has been used is the presentation of alcohol as the sole source of fluid. This procedure has the disadvantage of decreasing total fluid intake, which in turn probably decreases food intake. Also, only relatively low blood alcohol levels can be achieved, and they usually occur only at night when consumption is highest.

### ***Directions for Future Research***

Research using animal models to test for the behavioral teratogenicity of alcohol frequently appears to have been conducted without any theoretical framework or without consideration of the biochemical and physiological alterations that appear after prenatal exposure. One often feels that there is little rationale for choosing a particular test other than the fact that it has commonly been employed in behavioral research. Perhaps this "shotgun" approach was once necessary because of the scarcity of data on either humans or animals. However, for future research, behavioral teratologists using animal models should be cognizant of the types of behavioral manifestations noted in humans who were prenatally exposed to alcohol. Likewise, predictions of behavioral effects could be made in light of biochemical and physiological findings concerning FAS. This could allow investigators in these areas to predict which systems or structures might be affected by the types of behavioral anomalies reported. If these suggestions were followed, investigators with different areas of expertise and with vastly different techniques would be focusing on the same problems.

In deciding which behavioral tasks to use with animals, behavioral scientists must also be aware of the underlying characteristic that is being assessed. For example, a researcher interested in the effects of prenatal alcohol exposure on activity should perhaps use a variety of procedures and experimental models before making any conclusions. Similarly, if any firm conclusions about learning deficits are to be drawn, one should employ several tasks that presumably measure the same underlying construct and should also assess nonassociative factors. A more complete discussion of this problem can be found in an article by Barlow and Sullivan (1975).

Regarding future research trends, several important areas are untouched. Perhaps the most obvious gap in the literature is the lack of data on animals other than rodents. Use of rodents to screen for possible behavioral anomalies can quickly and economically provide extremely valuable data, but replicating these results with other species could prove illuminating. The physical teratogenicity of alcohol has been examined in dogs and miniature swine, and primate models are being developed. These species should be used in behavioral studies as well. Research with nonhuman primates seems particularly important consid-

ering the types of behavioral studies that could be conducted and the similarity of reproductive physiology between nonhuman primates and humans.

In most of the studies reviewed here, alcohol was administered to pregnant animals throughout gestation. One area for future research would be to determine the periods during gestation when the developing organism is most susceptible to the behavioral teratogenicity of alcohol. At present it simply is not known which types of behavioral anomalies result from alcohol exposure during different periods of development. Since there is evidence that reducing alcohol consumption during pregnancy improves the physical status of the infant, it seems imperative to investigate whether this also applies to behavioral dysfunction.

As mentioned earlier, some of the behavioral teratogenic effects of alcohol are age-dependent. For example, overactivity produced by prenatal alcohol exposure appears to diminish as the animal matures. Since many of the behavioral anomalies were noted in young animals, it is important to distinguish between transient and permanent effects. This can be accomplished by testing the offspring at various ages rather than choosing a single age to determine the presence of an effect.

Animal models also provide a tremendous opportunity to test various interventions. For example, behavioral assessment could be conducted after administering vitamin or mineral supplements to the mother or perhaps even to the offspring.

Another area that should be investigated is behavioral tests employing classical or Pavlovian conditioning techniques, since they permit a variety of cognitive functions to be examined.

Finally, animal models provide an opportunity to investigate genetic susceptibility to fetal alcohol effects. A variety of strains and selectively bred lines of rats and mice differing in alcohol-related phenotypes are available for study. It may be important to attempt to determine if certain genetic traits are associated with a risk of having an infant especially susceptible to fetal alcohol effects. A review of the possibility of genetic susceptibility to the teratogenic effects of alcohol is provided by Riley and Lochry (in press).

## ***Conclusion***

Perhaps it is best to conclude this overview of behavioral teratology studies on animals with this statement from Harbison and Braude (1975): "Exposure of the pregnant patient and newborn to abused drugs is a significant public health problem. The hazards of this exposure for future generations must be assessed and subsequent treatment of drug-induced effects programatically planned. The highest priority should be given to filling in the gaps in [our] knowledge. . ."

One of the gaps specifically mentioned was "drug induced long-term effects on behavioral development."

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## **Chapter 11**





# Drinking During Pregnancy: Effects on Human Development

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## Abstract

Fetal Alcohol Syndrome (FAS) is an abnormal pattern of growth and development that occurs in some children born to chronically alcoholic women. Children with FAS show a wide range of disabilities. Typically, FAS children are very small, have a similar facial appearance, and suffer major mental and motor retardation. The exact number of children affected by maternal alcoholism is unknown. Estimates are that one in every 750 to 1,000 live births may be FAS. Alcohol is suspected as the primary cause of the prenatal damage, although other factors such as heredity, nutrition, other drugs, and individual differences in susceptibility to alcohol may be involved.

Recent studies of moderate and heavy drinking women, compared with abstainers and light drinking women, indicate alcohol may negatively affect the developing fetus—even when the mother is not alcoholic. These effects include reduced physical growth, increased spontaneous abortions and stillbirths, and damage to the central nervous system, as reflected in the infant's behavior and postnatal development. There are many scientific limitations in investigations of human pregnancies. This means that precise cause-and-effect relationships seldom can be demonstrated and that the amount of alcohol that is "safe" to consume during pregnancy cannot be established. The need for long-term assessment of children whose mothers drink different amounts of alcohol, in different patterns (such as daily drinking versus binge episodes), is essential to better understand the association between drinking during pregnancy and children's wellbeing.

Prevention efforts and public information programs have started and offer promise as one means of preventing damage to the developing child. Objective evaluation of these efforts is critical, as well as encouraging innovative strategies to reduce alcoholism and alcohol abuse among women in the childbearing years.

## ***Introduction***

The fetal alcohol syndrome (FAS) is a pattern of abnormal physical and mental development detected with increasing frequency among children born to chronically alcoholic women. Over the past decade, several hundred case reports in the medical literature have provided a rich source of information about the wide range of effects observed in FAS children (Clarren and Smith 1978a). More important, the clinical recognition of this tragic form of mental retardation and its association with advanced stages of maternal alcoholism has led to systematic studies on the effects of alcohol use during pregnancy (Streissguth, Landesman-Dwyer, Martin, and Smith 1980) and efforts to prevent unnecessary alcohol-related birth defects (Little, Streissguth, and Guzinski 1980; Rosett et al. 1980).

The rapidly growing literature provides conclusive evidence that abusive drinking during pregnancy is potentially detrimental to fetal development, although there is much controversy about the actual mechanisms responsible for poor pregnancy outcomes. Longitudinal studies of "social drinking" detect increased physical problems or behavioral differences in children whose mothers drank moderately to heavily during pregnancy. However, these studies have not been able to identify the exact quantity of alcohol that is harmful, the critical period to avoid drinking, or the combination of factors such as smoking, use of other drugs, diet, or biological characteristics of the mother that significantly increase the risk of damage to an individual child.

This report focuses primarily on the most recent scientific and medical findings, and on their implications for future research and prevention efforts. Excellent reviews of earlier work (Clarren and Smith 1978a; Hinckers 1978; Hollstedt et al. 1977; Rosett 1976; Streissguth 1976b; Streissguth, Landesman-Dwyer, Martin, and Smith 1980; Weathersbee and Lodge 1978) and extensive bibliographies (from the National Clearinghouse for Alcohol Information, the Rutgers Center of Alcohol Studies, and the University of Washington Alcoholism and Drug Abuse Institute) are available elsewhere.

## ***Fetal Alcohol Syndrome (FAS) Defined***

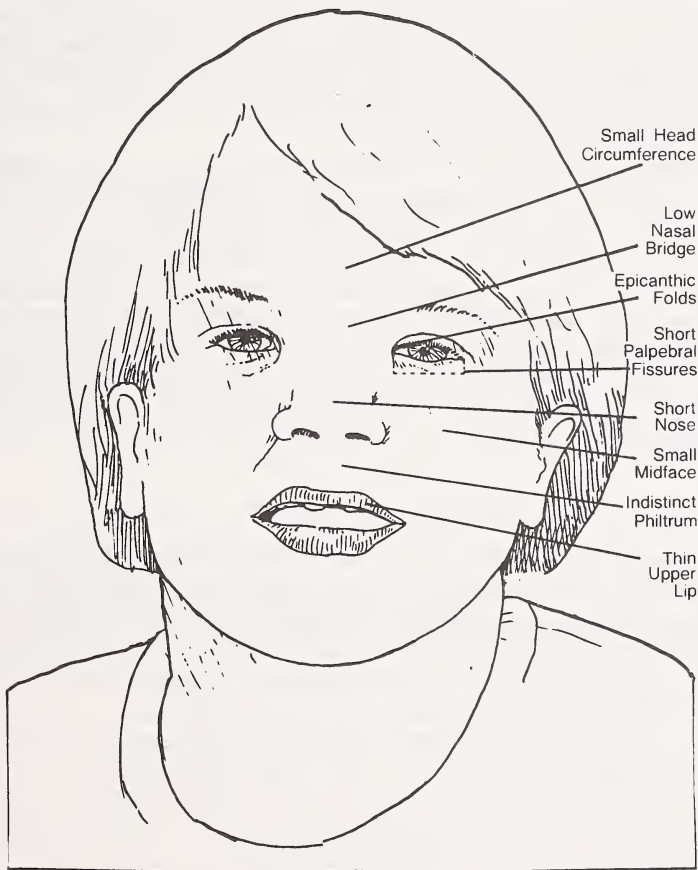
### ***Proposed Diagnostic Criteria for FAS***

In 1973, Jones and Smith used the phrase "fetal alcohol syndrome" to label the set of similar malformations they observed among failure-to-thrive children whose mothers were severely alcoholic (Jones and Smith 1973; Jones et al. 1973). The most salient and consistent characteristics of these children were: (1) mental retardation and poor motor development; (2) extreme growth deficiency before birth and throughout childhood, even with adequate diet; and (3) a typical facial appearance resulting from the constellation of relatively minor physical



features depicted in Figure 1 (from Streissguth, Landesman-Dwyer, Martin, and Smith 1980).

Figure 1. Typical Facial Appearance of an FAS Child



SOURCE:Reprinted from Streissguth et al. in *Science* (209:353-361, 1980) with the permission of the publisher. Copyright 1980 by the American Association for the Advancement of Science.

These primary FAS characteristics had been recognized independently and earlier by French investigators (Lamache 1967; Lemoine et al. 1968; Rouquette 1957). They subsequently have been confirmed by case reports throughout the world on children of all races and social classes (Clarren and Smith 1978a).

Table 1 summarizes the wide range of physical and functional abnormalities noted in clinically diagnosed cases of FAS. The features observed in the majority of FAS children are distinguished (by asterisks) from those observed less frequently. Many of the physical anomalies,

such as thin upper lip or small fingernails, are minor and are not unique to FAS. Similarly, many of the behavioral characteristics such as poor attention span, hyperactivity, or motor coordination problems appear often among mentally retarded children, regardless of the cause of their retardation. Although the features associated with FAS are diverse and range from mild to severe, this is not unusual; many birth defect syndromes—such as Down's Syndrome—show a comparable picture of individual differences (Warkany 1971). What is remarkable about FAS or other malformation syndromes is the similarity of the primary pattern or cluster of abnormalities in the children.

The proposed criteria for a diagnosis of FAS are (1) a history of chronic maternal alcohol abuse; (2) obvious growth retardation in weight, height, and head circumference from birth on; (3) marked impairment in intellectual and motor functioning, reflecting underlying damage to the central nervous system; and (4) a characteristic of phenotypic facial appearance, mostly attributable to reduced growth and development during the early embryonic period. (The fact that damage begins during the first trimester has led many European investigators to use the term "alcohol embryopathy" rather than FAS, e.g., Majewski et al. 1976.)

### *Milder Forms of FAS: Fetal Alcohol Effects*

For children of alcoholic women who show some but not all of the above criteria, "suspected fetal alcohol effects" has been proposed as an alternative diagnostic category (Clarren and Smith 1978a). Other expressions used to describe what may be milder forms of FAS include "prenatal effect of alcohol," "abnormalities suggestive of FAS" (Hanson et al. 1978), and "expanded fetal alcohol syndrome" (Shaywitz et al. 1978). In Germany, Majewski and his colleagues (Majewski et al. 1976; Seidenberg and Majewski 1978) have suggested three levels or gradations of FAS: severe (all of the criteria listed above), moderate (some functional impairment and physical signs), and mild (only one or a few minor signs). As with many other clinical disorders, there is no precise formula for the final diagnosis. Moreover, there is the danger that *any* child with some feature of FAS, such as small body size or hyperactivity, may be judged to have a problem that was caused by the mother's drinking during pregnancy. In many cases, it will be impossible to determine this or to separate the effects of heredity, nutrition, stress, and use of other drugs. The question of whether milder cases should be diagnosed warrants further study.

### *Controversies About FAS*

The literature of the past 6 years is filled with challenges to the belief that there is a fetal alcohol syndrome or that maternal alcoholism and alcohol use are the primary causes of the observed malformations (Dunn et al. 1979; El-Guebaly and Offord 1977, 1979; Johnson 1974;

**Table 1. Features Reported Among Clinical Cases of FAS**Perinatal Problems

Intrauterine Growth Retardation: Birthweight, Length, and Head Circumference Below the Third Percentile for Gestational Age<sup>1</sup>  
 Irritability, Tremulousness<sup>1</sup>  
 Hypotonia (poor muscle tone)<sup>1</sup>  
 Increased risk of perinatal mortality (stillbirths and neonatal deaths)  
 Small placenta  
 Premature birth  
 Respiratory distress syndrome  
 Abnormal umbilical cord: thin cord; single umbilical artery  
 Hypoglycemia (low blood sugar levels)  
 Hypocalcemia (low calcium)  
 Hyperbilirubinemia (high levels of serum bilirubin)  
 Seizures or seizure-like activity  
 Opisthotonos  
 Alcohol withdrawal syndrome  
 High-pitched cry  
 Fetopathia diabetica (form of diabetes)  
 Low Apgar score (at birth, indicates high risk of death)

Craniofacial Abnormalities

Short Palpebral Fissures (short eyeslits)<sup>1</sup>  
 Short Uprturned Nose<sup>1</sup>  
 Midface Hypoplasia (underdeveloped, small midface)<sup>1</sup>  
 Indistinct Philtrum (absence of or minimal ridges between nose and mouth)<sup>1</sup>  
 Hypoplastic Maxilla<sup>1</sup>  
 Thin Upper Vermilion Border of Lip<sup>1</sup>  
 Retrognathia in Infancy<sup>1</sup>  
 Micrognathia or Relative Prognathia in Adolescence<sup>1</sup>  
 Ptosis of eyelids (drooping eyelids)  
 Strabismus (poor coordination of eye muscles, such as cross-eyes)  
 Epicanthal folds (fold of skin on inner corner of eye)  
 Antimongoloid slant (eye slant rotating downward)  
 High arched palate (inside upper area of mouth)  
 Prominent lateral palatine ridges (elevated areas on top of mouth)  
 Cleft lip  
 Cleft palate  
 Wide mouth  
 Small teeth with faulty enamel  
 Myopia (near sightedness)  
 Microphthalmia (small eyes)  
 Blepharophimosis  
 Hypoplasia of nasal bridge (poorly developed bridge of nose)



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**Table 1. Features Reported Among Clinical Cases of FAS**


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Anteversion of nostrils (displaced nostrils)  
 Prominence of occiput (protruding back part of head)  
 Occipital flattening with balding (balding on flattened back of skull)  
 Narrow bifrontal diameter (small diameter across front of face)  
 Bilateral esotropia (when one eye focuses on objects the other turns in)  
 Tortuous retinal vasculature (abnormal vessel pattern in retina)  
 Pinnal anomaly (abnormal external ear)  
 Prominence of ears (noticeable ears)  
 Poorly formed concha (simple or underdeveloped hollow of external ear)  
 Low set, posteriorly rotated ears (ears below eye level, turned toward back of head)  
 Increase in nasolabial angle (increased spacing between nose and lips)

#### Postnatal Growth

Height and Weight Continue to be Below Third Percentile for Age (despite adequate caloric intake)<sup>1</sup>  
 Small Head Circumference<sup>1</sup>  
 Adipose Tissue Disproportionately Reduced (very thin)<sup>1</sup>

#### Central Nervous System Dysfunction

Mental Retardation, from Mild to Severe Levels<sup>1</sup>  
 Poor Motor Coordination, Including Abnormal Fine Motor Functioning<sup>1</sup>  
 Delays in Gross Motor Development<sup>1</sup>  
 Microcephaly (small brain size)<sup>1</sup>  
 Poor eye-hand coordination  
 Cerebral palsy, usually mild forms  
 Short attention span  
 Variable social quotient  
 Excessive friendliness to strangers  
 Learning disabilities (in absence of mental retardation)  
 Electroencephalographic (EEG) abnormalities  
 Seizure activity in childhood  
 Dysgenesis of neural structures—primarily abnormal migration of neuronal and glial elements  
 Hydrocephalus and other neural tube defects (related to incomplete or faulty closing of spinal cord and brain)

#### Cardiac Anomalies

Heart murmurs, notably in early childhood  
 Atrial septal defect  
 Ventricular septal defect  
 Tetralogy of Fallot  
 Patent ductus arteriosus

Table 1. Features Reported Among Clinical Cases of FAS

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Skeletal Abnormalities

Aberrant Palmar Creases<sup>1</sup>  
 Pectus excavatum  
 Limited range of motion of hip, knee, elbow, and/or other joints  
 Small nails  
 Polydactyly (more than the normal number of fingers or toes)  
 Camptodactyly  
 Clinodactyly (sloping or curving fingers)  
 Talipes equinovarus  
 Talipes calcaneovalgus  
 Shortened fifth finger  
 Overlap of fourth by fifth finger  
 Absence of interphalangeal creases  
 Low position of fifth toe  
 Increased interdigital skin folds (webbing)  
 Radioulnar synostosis  
 Infundibular thorax  
 Pectus carinatum  
 Bifid xiphoid  
 Klippel-Feil anomaly  
 Scoliosis (curvature of the spine)  
 Cryptorchism  
 Reduced skeletal age

Muscular Anomalies

Hernias of diaphragm, umbilicus, or groin  
 Diastasis recti abdominis

Cutaneous Anomalies (external, skin)

Hemangiomas (abnormally pigmented areas of skin)  
 Hirsutism in neonates (excessive hairiness, primarily on forehead)  
 Pigmented nevi  
 Preauricular skin tag  
 Accessory nipples (extra nipples)  
 Hypoplasia of nipples (underdeveloped nipples)  
 Wideset nipples  
 Presacral dimple

Renogenital Anomalies

Hypoplasia of labia majora (underdeveloped external genitalia in girls)  
 Hypospadias  
 Hydronephrosis  
 Small, rotated kidneys  
 Hepatic dysfunction; miscellaneous renal anomalies (abnormal liver functioning)  
 Biseptate vagina  
 Clitoromegaly

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<sup>1</sup> Features observed in majority of FAS cases.

Mendelson 1978, 1979; Thompson 1979; V'eghelyi et al. 1978). Unfortunately, a considerable portion of the criticism and disbelief reflects a lack of understanding of the fundamentals of teratology (the branch of science that studies the effects of substances on prenatal development), inexperience with syndromes of dysmorphology (a highly specialized aspect of pediatrics concerned with identifying malformation patterns, which often are very complex and subtle), and incomplete or spotty review of the rapidly expanding literature.

On the other hand, some of the skepticism is justified since serious questions remain unanswered. The most frequently raised questions and the best available answers are as follows.

1. Is FAS really a unique syndrome, or does it overlap with other birth defects to such a degree that its clinical recognition is not reliable?

FAS appears to be recognized easily by dysmorphologists who have had extensive experience with this syndrome. Many of the children are identified on the basis of their physical features and performance even before a history of maternal alcoholism is known (Jones and Smith 1978; Lemoine et al. 1968). Admittedly, other syndromes share characteristics with FAS and sometimes cause difficulty in initial diagnosis (Bianchine and Taylor 1974; Hall and Orenstein 1973; Lowry 1977; Mulvihill and Yeager 1976). These syndromes include Noonan, Cornelia de Lange, Dubowitz, Grob, Gruber, Smith-Lemli-Optiz, familial blepharophimosis, fetal hydantoin, Klippel-Feil anomaly, and the trisomy syndromes. However, FAS can be differentiated from all of these (Hinckers 1978; Mulvihill et al. 1976).

Unfortunately, careful studies to determine the accuracy of FAS diagnosis or the agreement among different clinicians have not been conducted. There is a definite need to encourage systematic and comprehensive clinical evaluation of all suspected FAS cases. If this could be accomplished, a more precise picture of FAS and its various manifestations would become available.

2. Is FAS always associated with a history of chronic maternal alcoholism, or could a very heavy binge episode or excessive drinking by a nonalcoholic woman produce an FAS baby?

So far, there is no documented case of the full-blown FAS without a history of chronic maternal alcoholism (Clarren and Smith 1978*b*). Tragically, many of the mothers die shortly after the birth of their FAS children or are unable to care for their offspring (Olegard et al. 1979; Pierog et al. 1979; Streissguth 1976*a*). Nonalcoholic women or early-stage alcoholics have never been known to produce children with FAS. This does not imply that all nonalcoholics are safe from any harm



caused by drinking during pregnancy (see section on social drinking), but it emphasizes that the maternal factors involved in FAS are likely to be complex and cumulative, just as the advanced stages of alcoholism are.

Two children with FAS features whose mothers did not drink alcohol (self-report) are described in the literature. One child was born to recovering alcoholic parents (Scheiner et al. 1979). The other was born to a woman who abused solvents (Toutant and Lippmann 1979). Close review of the case reports indicates neither child had the complete set of FAS signs (Smith and Graham 1979).

3. Is prenatal exposure to alcohol the primary cause of FAS, or are there multiple factors?

Based on human investigations, alcohol alone cannot be singled out as the direct cause of FAS. There is no doubt that alcohol readily crosses the placental barrier, enters the fetal circulatory system almost instantaneously (Cook et al. 1975; Idanpaan-Heikkila et al. 1972; Waltman and Iniquez 1972), remains in the infant for a considerable time (Hollstedt et al. 1977; Wagner et al. 1970), and can depress central nervous system functioning in the fetus and newborn (Kim and Hodgkinson 1976; Lewis and Boylan 1979). What is uncertain is whether the severe damage seen in FAS is caused by alcohol, its metabolites such as acetaldehyde (O'Shea and Kaufman 1979; V'eghelyi et al. 1978), imbalance in maternal or fetal homeostasis (Weathersbee and Lodge 1979), or the interactive effects of alcohol and other risk factors—such as smoking and malnutrition—or genetic factors (Streissguth, Landesman-Dwyer, Martin, and Smith 1980). For example, women who suffer from advanced stages of alcoholism may represent a biologically or genetically distinct group (V'eghelyi et al. 1978) whose children may be more susceptible to the effects of alcohol (Mulvihill et al. 1976).

Experimental animal studies, reviewed by Randall and Riley elsewhere in this chapter, provide important evidence about alcohol's effects. Alcohol alone can alter cell division and differentiation under highly controlled laboratory conditions (Brown et al. 1979). Moreover, numerous animal studies detect significant physical or behavioral differences between offspring exposed to alcohol prenatally and unexposed controls. There are, however, substantial differences between human and animal pregnancies, as well as between the full FAS and other alcohol-related effects.

4. Is there a continuum of effects from severe to mild?

A continuum of effects appears consistent with the clinical evidence both on FAS and on other mental retardation and malformation syndromes. FAS children with the most severe physical signs typically show the greatest degree of mental impairment (Dahaene et al. 1977; Majewski et al. 1976; Seidenberg and Majewski 1978; Streissguth, Herman, and Smith 1978a). Relatively few FAS children have been studied as they grow older. Although a few children improve in IQ performance, most continue to function at the same level of retardation even when good foster care and special school programs are provided (Dehaene et al. 1977; Seidenberg and Majewski 1978; Streissguth, Herman, and Smith 1978b).

Generally, children of alcoholics (usually males) are at risk for a variety of problems, many thought to be caused by heredity or the home environment (El-Guebaly and Offord 1977, 1979). Two studies compared children of alcoholic women to control children whose mothers were not alcoholic but were similar to the alcoholics in age, marital status, educational level, family size, socioeconomic status, and other characteristics. Both studies found that the alcoholics' children had significantly lower IQs (Jones et al. 1974; Streissguth et al. 1979), although they usually were not retarded and did not have FAS. Other differences reported include hyperactivity and minimal brain dysfunction (Cantwell 1972; Morrison and Stewart 1971; Shaywitz et al. 1978), abnormal brain wave patterns (Havlicek et al. 1977; Olegård et al. 1979), brain malformations (Clarren et al. 1978; Peiffer et al. 1979), lowered birthweight (Little, Streissguth, Barr, and Herman 1980; Olegård et al. 1979; Russell 1977), cardiac defects (Dupois et al. 1978; Loser and Majewski 1977), and cerebral palsy (Olegård et al. 1979). As early as 1899, Sullivan (1899, 1900) reported significantly increased stillbirth and infant death rates for alcoholic women in the Liverpool jail, compared to their nonalcoholic female relatives.

Three important issues are related to the notion of a continuum of FAS: What is the lower limit (i.e., the mildest form) of FAS? Should the effects of social drinking during pregnancy be mixed in with those of maternal alcoholism or be kept separate? And how permanent or treatable are the handicaps associated with FAS?

5. If there is a continuum of effects, is the severity of damage related to the amount of alcohol the mother consumed?

The amount of alcohol a woman drinks may not be as critical as other factors. For example, the *stage* of maternal alcoholism (based on degree of alcohol dependence and severity of alcohol-related medical and social problems) may predict FAS risk better than how much a woman drinks during pregnancy (Jones and Smith 1978; Seidenberg and Majewski 1978). Another view is that equal amounts of alcohol may have very different effects, largely depending on the mother's acetaldehyde levels (V'eghelyi et al. 1978). Further study in this area is extremely important to understanding the cause of FAS.

Accurate information about the quantity of alcohol consumed is extremely difficult to obtain, particularly from alcoholics who may have

substantial memory loss and denial. Major questions regarding the critical period for drinking during pregnancy, the pattern of alcohol use (e.g., binge drinking episodes versus daily use), and problems associated with drinking are extremely difficult to answer in human studies, although notable advances have been made in collecting maternal data throughout pregnancy (Sokol 1980). A neglected area of study has been the role of the father, his alcohol use, and his family history of alcoholism.

### ***Prevalence of FAS***

The number of children with FAS in the United States is unknown. Several studies of pregnancy outcome do provide indicators of the incidence, however. A study in Sweden detected 1 FAS infant per 600 live births (Olegard et al. 1979). In a Seattle sample, the rate was 1 per 750 (Hanson et al. 1978). And in Northern France, 1 per 1000 births showed the full FAS (Dehaene et al. 1977). In the French study, 1 per 400 infants had at least a mild form of FAS; the Swedish study reported a rate of 1 per 300. If these estimates of incidence hold true for the general population, FAS would be one of the most common malformation patterns associated with mental retardation, along with Down's Syndrome and neural tube defects (Center for Disease Control 1979).

There is very limited information about an alcoholic woman's risk of bearing an FAS baby. In studies of mostly low income, chronically alcoholic women, 26 to 33 percent gave birth to an FAS child (Jones et al. 1974; Majewski et al. 1976; Olegard et al. 1979). However, no systematic definition was used for alcoholism or for selecting the population to be studied. In the medical literature there is an overrepresentation of poor, minority children with FAS—most notably Native Americans and blacks. The reasons for this are not clear but may relate to a combination of social class and biological factors (Streissguth, Landesman-Dwyer, Martin, and Smith 1980).

### ***Drinking During Pregnancy: Practices and Attitudes***

Women between the ages of 18 and 34, the primary childbearing years, constitute nearly one-fifth of the nation's "heavy drinkers," defined as (a) often consuming five or six drinks at a time plus (b) having an average of at least one drink a day (Chambers and Griffey 1975). This is higher than expected based on the number of women in this age range. A recent survey by Opinion Research Corporation (1979) indicates that pregnant women are somewhat less likely to drink alcoholic beverages (42 percent) than are nonpregnant women (59 percent), although 5 to 7 percent of pregnant women admit to getting drunk and to drinking five or more drinks on one occasion. Surprisingly,



at least 80 percent of the respondents (representative of the U.S. population) already felt that women should not drink when pregnant. Moreover, the amount of alcohol they judged to be "safe" during pregnancy is relatively small—less than half a drink a day. They considered three times this amount safe for nonpregnant women to drink daily (Opinion Research Corporation 1979).

Alcohol use is known to decrease dramatically during pregnancy (Little et al. 1976; Streissguth et al. in press). The primary reasons women give for this decrease are that alcoholic beverages do not taste as good as before, make them feel sick, or may jeopardize the well-being of their child (Little et al. 1976). It is interesting that this concern for fetal welfare existed *before* public knowledge about the fetal alcohol syndrome. For some alcoholic women, binge episodes may increase during pregnancy, even though the total amount of alcohol consumed is reported to be less (Little and Streissguth 1978).

### ***Social Drinking During Pregnancy***

The discovery of FAS triggered scientific inquiry into the effects of social or moderate drinking during pregnancy. Since 1974, at least six prospective studies have focused on the question, "Is social drinking during pregnancy harmful?" and several epidemiological studies of pregnancy outcome have provided relevant findings. In a pilot prospective study started in 1974 at Boston City Hospital, 633 women were interviewed and 322 babies were examined (Ouellette and Rosett 1976; Ouellette et al. 1977; Rosett et al. 1976). These inner city women generally were at high risk for pregnancy problems, because of their low socioeconomic status, poor nutrition, heavy smoking, and other maternal characteristics. In a later Boston study, 1,991 women were interviewed between 1977 and 1979 and 1,719 newborns were assessed (Alpert et al. 1981).

Two pregnancy and health studies have been conducted in Seattle. The first involved 801 women. Birth weights were analyzed in a selected sample of 263 infants (Little 1977; Little et al. 1976, 1977) and behavioral development was assessed in 130 children at 4 and 5 years of age (Landesman-Dwyer et al. 1981). The second Seattle study is the most comprehensive to date in its assessment of pregnancy outcomes in 1,529 women and its detailed, repeated evaluation of 500 children from birth on (Streissguth et al. in press). An epidemiological study at Loma Linda, California, has collected data on more than 12,000 pregnancies (Kuzma and Phillips 1977) and has conducted preliminary analyses for 5,189 infants (Kuzma 1980). Some findings from the first year of a new study in Cleveland have been reported, involving interviews with 2,913 pregnant women (Sokol 1980; Sokol et al. 1981).

The epidemiological studies that have analyzed for effects of alcohol use, although this was not their major goal, include a French investiga-

tion of more than 9,000 pregnancies (Kaminski et al. 1978, 1979), a California study of more than 32,000 pregnancies (Harlap et al. 1979), a New York study that utilizes a case-control design (Kline et al. 1980), and a Cleveland study of more than 12,000 pregnant women (Sokol et al. 1980).

These investigations differ considerably in the number and type of women studied, measurement of alcohol use and other pregnancy habits, assessment procedures for infants, and statistical approaches to analyzing the data. Despite these differences, the findings are remarkably consistent: heavier alcohol use is associated with adverse effects on pregnancy, even after other factors such as maternal age and smoking are controlled for (Landesman-Dwyer 1979; Little 1980; Streissguth, Landesman-Dwyer, Martin, and Smith 1980).

Before reviewing the findings, some cautionary statements are warranted.

First, all studies have relied on self-reporting of alcohol consumption. Clearly, human recall is incomplete and a select group may either knowingly or unknowingly underreport their alcohol consumption. Generally, it is assumed that few women overestimate their alcohol intake. Although there are standardized ways to quantify alcohol use (Little et al. 1977; Streissguth, Martin, and Buffington 1977), it is important to note that women categorized as "heavy drinkers" by one method frequently are not labeled "heavy drinkers" by another method (Little et al. 1977).

Second, drinking is not an isolated behavior randomly distributed across the population. Women who drink, particularly those who drink heavily, are different from those who abstain or drink very infrequently. Typically, women who drink heavily tend to be older, to have had more prior pregnancies, to be of lower socioeconomic status, to weigh more, to receive less prenatal care, and to smoke and use other drugs more—although these differences vary somewhat among the studies (Kaminski et al. 1978; Rosett et al. 1976; Sokol et al. 1980; Streissguth, Martin, and Martin; 1978). Therefore, any analysis of the effects of maternal drinking on pregnancy outcome should consider the potential contribution of these other factors.

Third, there is always a question of what is harmful. Physical malformations, reduced body size, stillbirths, and neonatal deaths are undeniably negative pregnancy outcomes, but when it comes to behavior there are no standards for judging how much crying or sleeping or responding to the environment is "good," or at what point deviation from the norm represents a potential handicap for a given child. The field of behavioral teratology is comparatively new, and there are many difficulties in relating subtle behavioral differences in children to specific intrauterine conditions (Kolata 1978). Since there is no agreed-upon way to evaluate all newborns and young children, many different outcome measures have been used. Ultimately, the strength of the behavioral findings will rely upon the degree to which they are

replicated—that is, whether other studies, using somewhat different test measures and different subjects, find similar effects (Little 1980).

### *Physical Development and Survival of Offspring*

One of the most noted effects is that increasing maternal alcohol use or misuse is related to decreased growth of the infant, as reflected in birthweight, length, and head circumference (Kaminski et al. 1978; Little 1977; Ouellette et al. 1977; Sokol et al. 1980; Streissguth et al. in press). For birthweight, the estimated decrement ranges from 60 to 160 grams for infants whose mothers reported drinking an average of two to three drinks a day. All of the studies report that the heavier drinking women who also smoke cigarettes are at even higher risk of delivering small babies, and their babies may face increased problems in adapting to postnatal life (Landesman-Dwyer and Emanuel 1979).

In the French study, the risk of stillbirths was increased two and a half times for women who reported drinking an average of three or more drinks a day. The risk was even greater when the mothers also smoked, came from lower socioeconomic classes, had more prior pregnancies, or were older (Kaminski et al. 1978). The California study also detected a significant increase in spontaneous abortions, which increased with the amount of reported maternal drinking even after adjusting for important variables correlated with drinking (Harlap et al. 1979). Similarly, the study in three New York hospitals reported an increase in spontaneous abortions, with daily drinkers having a fivefold increase in their risk (Kline et al. 1980).

The findings about physical malformations are limited. Only one published study evaluated minor malformations systematically, particularly as related to FAS (Hanson et al. 1978). In the large Seattle study, children born to heavier drinkers were more likely to show a pattern of minor anomalies suggestive of FAS, although no one abnormality appeared for all infants. Autopsies of stillbirths and neonatal deaths revealed a characteristic brain malformation (leptomeningeal neuroglial heterotopia) among offspring of chronic alcoholics and several binge drinkers (Clarren et al. 1978). In the Boston pilot study, routine pediatric exams detected an increase in the overall rate of major and minor birth defects: heavy drinkers (see definition under Drinking During Pregnancy) had a rate of 37 percent compared to 14 percent for moderate drinkers and 9 percent for light drinkers (Ouellette et al. 1977). In a study of clinically recognized alcohol abusers, Sokol et al. (1980) found increased congenital abnormalities, although stillbirths and perinatal mortality were not affected in this sample of 204 women.

### *Behavioral Effects of Intrauterine Alcohol Exposure*

One of the most important questions is whether the behavioral and mental development of children is compromised by moderate to heavy drinking during pregnancy. In every published study, some behavioral



differences have been detected between children born to smoking or nonsmoking heavier drinkers and those born to lighter drinkers and abstainers (Little 1980). The behavioral outcomes cover a wide range and are of two kinds: (1) those that rely on routine clinical tests and observations and (2) those that are designed to assess highly specific aspects of behavioral functioning under controlled or laboratory conditions.

The clinical measures have the advantages of being easy to obtain on large groups of children and of providing an index of how obvious the differences are to regular health care practitioners. In contrast, the controlled measures usually are difficult to obtain and require specialized equipment and highly trained technicians as well as elaborate procedures to insure scientific rigor in collecting and analyzing the data. However, controlled measures provide a unique opportunity to detect very subtle or subclinical differences among children, often in functional areas that are not evaluated during the routine health care of infants and young children.

The Boston pilot study and the Seattle studies have included both clinical and laboratory measures on the children's behavioral development, and are the only prospective studies that have published findings about behavior.

In the Boston pilot study, examination by a pediatric neurologist revealed that infants whose mothers drank heavily were significantly more likely to be jittery, to have poor muscle tone (hypotonia), and to have poor sucking ability, compared to babies whose mothers were classified as moderate drinkers or abstainers (Ouellette and Rosett 1976; Ouellette et al. 1977). The newborns did not differ in their Apgar ratings at 1 or 5 minutes after birth. (The Apgar scale is a standard way of evaluating an infant's status after delivery in terms of muscle tone, color, respiration, heart rate, and reflex irritability.)

On the third day of life, 31 infants were carefully studied by 24-hour continuous recording of their sleep and activity cycles. Fourteen of the infants were born to heavy drinkers, 8 to women who drastically reduced their alcohol use after counseling, and 9 to women who were light drinkers or abstainers (Rosett et al. 1979). The recording procedures permitted analysis of the amount of time infants spent in various stages of sleep or wake behavior, how easily infants were distracted by caretaking procedures, and how well organized their state regulation appeared (Sander et al. 1977). The major findings were that infants prenatally exposed to greater amounts of alcohol slept less, had a poorer quality of quiet sleep, showed more disrupted sessions of quiet sleep, and had more frequent major body movement. The investigators caution that their findings may have limited generalizability, however, because the infants in the heavy drinking group were not well matched to those in the other groups and the sample was very small.

In the Streissguth, Landesman-Dwyer, Martin, and Smith (1980) study, a group of 500 infants was selected for in-depth behavioral study at birth. On the first day of life, between 8 and 32 hours of age, all

infants were given a standardized examination, the Brazelton Neonatal Assessment Scale, under rigorous conditions by trained examiners (Streissguth, Martin, and Barr 1977). This clinical tool is popular because infants are evaluated on many different items (about 30) including reflexes; responsiveness to auditory, visual, and social stimuli; habituation to repeated stimuli; and characteristics such as consolability and cuddliness. Data from the Scale were factor-analyzed and yielded six readily interpretable factors. Two of these six factors showed a significant relationship to maternal alcohol use during pregnancy. One factor was "habituation," which measures the newborn infant's ability to shut out redundant stimuli—that is, to stop responding to the same external event when sleeping lightly. The repeated stimuli included a bell ringing, a rattle shaking, and a flashlight shining on the infant's eyes for ten consecutive trials. Infants prenatally exposed to relatively greater amounts of alcohol were not as capable of tuning out these redundant stimuli.

The second factor related to maternal alcohol intake was labeled "low arousal." Infants whose mothers drank more were easier to console or to quiet, had more frequent state changes, and were characterized by low levels of excitability. These findings persisted even after statistical adjustment for the effects of nicotine, caffeine, parity, sex, and age of the infant. Moreover, maternal alcohol scores were better predictors of performance on the standardized exam than either nicotine or caffeine scores were.

A separate observational study of 124 of these infants also was conducted on the first day of life (Landesman-Dwyer et al. 1978). Naturalistic observations were recorded of the infants' behavior before, during, and after the Brazelton exam. A "baby behavior code" was developed for this study, consisting of separate dimensions that allowed coding of all behaviors. These dimensions were external stimulation, eye movements, facial expressions, vocalizations, head position, and body and limb movements. An electronic data acquisition system was used to record the frequency, duration, and actual sequence of all behavior. The significant main effects of maternal alcohol use on newborn behavior were (a) increased body tremors; (b) increased nonalert wake state; (c) increased head orientation to the left, an atypical position in newborns; (d) increased hand-to-mouth behavior; and (e) decreased vigorous body activity.

All of the above findings were controlled for the possible effects of maternal smoking, birthweight, sex of child, and birth order. During the study period, one newborn with a clinical diagnosis of fetal alcohol syndrome manifested deviant behavior in each of the above categories, all in the same direction as detected for the offspring of moderate to heavy social drinkers. This suggests that there may be some specificity of the behavioral effects associated with prenatal exposure to ethanol; that is, the effects of moderate maternal alcohol intake appear to reflect a mild or very subtle pattern of dysfunction similar to that seen in affected offspring of chronic alcoholics. Furthermore, these alcohol



effects are quite distinct from those associated with either heavy maternal smoking or low birthweight.

Next, the Seattle infants were exposed to an operant conditioning model on the second day of life (Martin et al. 1977). Approximately one-half of the subjects received reinforcement for head turning, while the remainder were reinforced for sucking. For both head turning and sucking, a similar pattern of results was obtained: infants whose mothers *both* smoked and drank more heavily during pregnancy performed significantly worse in this learning situation. However, prenatal exposure to alcohol alone did not significantly lower performance. In addition, Martin et al. (1979) evaluated the sucking patterns of 151 infants by electronically recording amplitude, frequency, and duration of sucking. They found that infants whose mothers smoked or were moderate to heavy drinkers had significantly weaker sucking ability. This is particularly important since FAS babies are known to have feeding difficulties and to have poor sucking ability.

In addition to the detailed neonatal studies, the medical records of 1,439 subjects were reviewed (Streissguth, Barr, Martin, and Woodell 1978). Increasing amounts of maternal alcohol intake were associated with lower Apgar scores at 1 minute of age. Seven percent of the infants of the heaviest drinking drinkers (316 mothers) had Apgar scores below 3—a score that is alarming in any delivery room. Of the infants whose mothers drank at levels considered “safe,” only 3 percent had scores of 3 or less. Offspring of heavier drinkers also had more fetal heart rate abnormalities (brachycardia and variable deceleration) and an increased need for ventilatory resuscitation during the first few days of life.

Collectively, the above findings suggest that the central nervous system may be affected by exposure to alcohol, even when mothers are not alcoholic. A critical issue is whether these effects are long-lasting and, if so, to what extent the children's lives are altered. Only two followup studies have been reported. Streissguth, Barr, Martin, and Herman (1980) found that the developmental progress of infants, as measured by a standardized exam of mental and motor abilities, was related to the amounts of alcohol their mothers reported drinking; the decrement in functioning at 8 months of age was small but significant. An observational at-home study of 4-year-olds whose mothers had been studied during pregnancy by Little (1977) indicated that attention span, fidgetiness, and compliance with parental commands were different for children whose mothers drank an average of one drink a day during pregnancy, compared with children whose mothers drank less (Landesman-Dwyer et al. 1981). Both studies controlled for important factors such as smoking, maternal age and social characteristics, and birth order of children. The investigators interpret their findings conservatively, pointing out that there could be influences from the postnatal environment and other factors not measured. However, two separate studies of children's home environments and maternal behavior failed to detect any differences in parenting style or stimulation



of the children that were correlated with maternal drinking habits (Landesman-Dwyer et al. 1981; Ragozin et al. 1978). Also, the few long-term behavioral effects reported are small and by themselves probably do not indicate impairment of the children's general functioning. Additional followup studies clearly are needed.

None of the human studies can answer the vital question, "How much is safe to drink?" The reasons relate to those discussed earlier, since accurate measurement of intake is not available and multiple factors occur in conjunction with alcohol use. The two Seattle studies, which focus on women who are generally healthy and whose drinking levels are quite low, have detected some subtle effects in the children of women who claim to drink only an average of one or two drinks a day and never have binges or get drunk. Equally important is the question about timing. Theoretically, the early embryonic period (in the first trimester of pregnancy) is the most vulnerable one to major disruption of the tissue systems, although the third trimester is the period when influences on birthweight are likely to occur.

### ***Prevention of Fetal Alcohol Damage***

Major efforts to inform the public about FAS have been made even in the absence of some important scientific evidence concerning the exact mechanisms responsible for the syndrome or the milder effects of maternal drinking. Encouraging results are reported by Rosett et al. (1980), indicating that clinical counseling of heavy drinkers during pregnancy may result in decreased alcohol use with potential benefits to the infants. Recently, a model prevention program was described by Little, Streissguth, and Guzinski (1980), although it is too early to evaluate the effectiveness of alternative prevention strategies. Given the long and variable history of prevention efforts related to smoking during pregnancy (Landesman-Dwyer and Emanuel 1979), considerable attention to scientific inquiry in this area is warranted. This is a highly controversial area, with much debate about the potential efficacy of traditional treatment and public information efforts and about the ethics of various interventions (Olegard et al. 1979; Pierog et al. 1979; Rosett et al. 1980). Unfortunately, early efforts to encourage abstinence led to the prescription of disulfiram (Antabuse), which caused fetal limb deformities and sometimes fetal death (Nora et al. 1977).

### ***Summary and Recommendations***

Three major facts emerge from the literature:

1. The fetal alcohol syndrome is a definite pattern of malformation and mental impairment associated with advanced stages of maternal alcoholism.

2. Children born to alcoholics are at risk for a wide range of problems, including partial or milder forms of FAS.
3. Women who are moderate to heavy drinkers tend to have babies who are smaller and who show some mild behavioral differences in comparison to controls. Other correlates of social drinking, such as increased stillbirth rates, have been noted as well.

Considerable controversy remains about the criteria for diagnosing FAS, as well as the estimated incidence of FAS and the mechanisms responsible for intrauterine damage. High priority is warranted for research in the following areas of uncertainty:

1. Epidemiologic studies are needed to determine the actual incidence and prevalence of FAS among different populations.
2. Clinical studies are needed to improve the precision of the clinical diagnosis of FAS and to determine what constitutes partial FAS.
3. Interdisciplinary studies are needed to determine (a) the biological and psychological factors that differentiate alcoholic women who have FAS children from those who have normal children and (b) the mechanisms responsible for damage to the embryo and the fetus.
4. Prospective studies also are needed to replicate findings about the effects of social drinking during pregnancy, using large study populations and better measurements of alcohol use and metabolism. Followup of children's behavioral and physical development will be vital in such studies.
5. Other factors that might interact with alcohol to affect pregnancy require study. They include such factors as paternal effects, prior life experiences, stress, use of other substances, diet, and prenatal care.

Studies like these usually require major efforts by researchers from diverse disciplines who are experienced in the study of alcoholism, pregnancy outcomes, or child development. Ultimately, many conclusions will rely on evidence from controlled studies with animals, with parallel or consistent observations in humans.

Finally, though the development of multiple prevention strategies does not need to await further scientific data on FAS, the impact of such strategies must be measured objectively and systematically.

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